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ADRENOGENITAL SYNDROME DUE TO CONGENITAL VIRILIZING ADRENAL HYPERPLASIA

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THIS report is a review of fourteen cases of adrenogenital syndrome of the congenital type which have come under the authors' care in part or completely within the past ten years. These cases will be reviewed in a manner which is intended to point out the important clinical and laboratory features of the syndrome. The medical, psychological, and surgical aspects of the management of this condition will be discussed.

DESCRIPTION OF THE SYNDROME

Adrenogenital syndrome of the congenital type is a familial condition in which excessive androgen secretion occurs in homozygous offspring as a result of an inborn error in metabolism. The excessive secretion of androgen originates during the gestational period and continues throughout life if not treated. Accurate clinical and anatomical descriptions of the disease have been available since the early years of this century.[1, 2] However, it is only since the discovery by Wilkins and associates[3] of the efficacy of cortisone in controlling this abnormal secretion, thus enabling these individuals to lead a near-normal life, that interest in this condition has become widespread. Independently from Wilkins, Bartter and co-workers[4] in the same year reported that cortisone decreases the 17-ketosteroid excretion in this condition.

The abnormal secretion of androgen with its virilizing effects exerts a profound influence on sexual development and somatic growth. In the female there occurs the syndrome of female pseudohermaphroditism, and, in the male, macrogenitosomia precox.

The female pseudohermaphrodite may be described as follows:

The anatomical abnormalities are confined mainly to the external genitalia and somatic growth. The genitalia of the newborn infant frequently presents the picture of a male with hypospadias and undescended testes. The clitoris may be enlarged to the size of a small or normal penis. The so-called hypospadic urethra in reality

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TABLE I

PATIENT	AGE ON ADMISSION	SEX AND RACE	ADMISSION DATE (MO.-YR.)	PUBIC HAIR	CLITORIS HYPERTROPHIED	URETHRA	INTROITUS	PENIS	TESTES	SALT-LOSER	AGE AT DEATH
R. H.*	12 days	WM	8-47	Absent		Normal		Normal	Normal	+	16 days—in crisis
R. L. H.*	1 month	WF	1-49	Absent	+	Vaginal	Otherwise normal			+	5 weeks—in crisis
J. B.**	6 weeks	WM	2-50	Present 6 months		Normal		Hypertrophied pigmented	Hypertrophied	+	1 year—in crisis
B. A.	19 days	NF	8-50	Absent	+	Normal	Absent			+	2 months—in crisis
D. H.***	6 years	WF	5-52	Present 1 year	+	Normal	Normal				
R. R.	6 years	WM	8-52	Sparse 6 years		Normal		Hypertrophied	Small	+	
H. T.	3½ years	WM	8-53	Present 3½ years		Normal		Hypertrophied	Infantile	+	
K. S.	4½ years	WF	1-54	Present 2½ years	+	Normal	Normal				
C. B.**	Birth	WF	2-54	Absent	+	Partial clitoral	Absent			+	
B. W.	Birth	NF	11-54	Absent	+	In urogenital sinus	Urogenital sinus			+	1 month—aspiration pneumonia
S. P.	1 month	NF	12-55	Absent	+	In urogenital sinus	Urogenital sinus				
P. H.***	7 months	WF	7-56	Present 6 months	+	In urogenital sinus	Urogenital sinus				
A. W.	2 weeks	WF	12-56	Absent	+	Vaginal	Partial coalescent labia			+	
J. J.	4 months	WF	7-57	Absent	+	Normal	Partial coalescent labia			+	

*Siblings.
**Siblings.
***Siblings.

is the external opening of the urogenital sinus into which the female urethra and vagina enter. The labia are fused in the midline to a variable degree. Other virilizing manifestations which appear somewhat later include precocious growth of pubic hair, acneiform rash, and facial hirsutism.

Paralleling the increase in somatic growth, there is advanced bone age with early closure of the epiphyses. These individuals, therefore, reveal advanced longitudinal and somatic growth during early life, but eventually end up shorter than normal with a masculine type of body configuration. Menarche and all other signs of secondary female sexual maturation do not develop.

In the male there occurs precocious development of the secondary sexual characteristics along the lines of his true sex. However, this does not represent a true sexual precocity, because the testes remain underdeveloped, small and soft, and are nonfunctional. The major androgenic effects are precocious growth of the penis and prostate, hyperpigmentation of the scrotum, and early growth of pubic hair. This type of sexual development has been termed macrogenitosomia precox. With respect to somatic and skeletal growth, the pattern is comparable to that of the female pseudohermaphrodite. This excessive muscular growth and short stature have resulted in these individuals being called "Infants Hercules."

It is important to recognize that in association with this excessive androgen secretion there occurs an abnormally high excretion of urinary 17-ketosteroids, which constitutes the single most dependable laboratory evidence to support the diagnosis. Normally the 24-hour urinary 17-ketosteroid output does not exceed quantities of 1 mg. until the sixth to eighth year of life. However, in congenital adrenal hyperplasia, quantities higher than those found in normal adults (up to 15 mg. per 24 hours) have been observed; quantities exceeding 50 mg. per 24 hours have been found only rarely.

In addition to the above virilization process, congenital virilizing adrenal hyperplasia is sometimes associated with abnormal salt losses, leading to symptoms resembling adrenal cortical insufficiency (Addison-like syndrome). The abnormal salt loss is characterized by profound dehydration which is difficult to treat without the use of steroids and large quantities of salt. Vomiting and diarrhea may be a prominent feature of adrenal cortical insufficiency and a contributing factor in the production of shock resulting in death. The salt-losing syndrome resembles aldosterone insufficiency with the blood plasma revealing a low level of sodium, chloride, bicarbonate, and an elevated level of potassium. Hypoglycemia occurs only rarely.

REPORT OF CASES

Pertinent information concerning these cases is summarized in Table I. It will be observed that the number of female pseudohermaphrodites is approximately three times as great in this series as the number of males with macrogenitosomia precox. We wish to emphasize the high familial incidence in this series, and this will be enlarged upon in the discussion.

Ten out of fourteen cases presented findings of the salt-losing syndrome. These included all four males and six out of ten females. Three cases, two

of which were salt-losers, occurred in Negroes. The clinical and biochemical abnormalities of this electrolyte disturbance will be elucidated further in the discussion.

Anatomical Anomalies.—Typical cases of *female pseudohermaphroditism* are illustrated by Figs. 1 and 2. The case of D. H. (Fig. 2), first seen at 6 years of age, showed evidences of marked virilization due to prolonged influence of excessive androgens.

The clitoris in all of these cases was uniformly enlarged at the time of our first observation. Six patients were observed during the neonatal period, and the remaining were seen for the first time at 6 years, 4½ years, 7 months, and 4 months of age, respectively. An erroneous assignment of sex at birth and prior to our first ob-

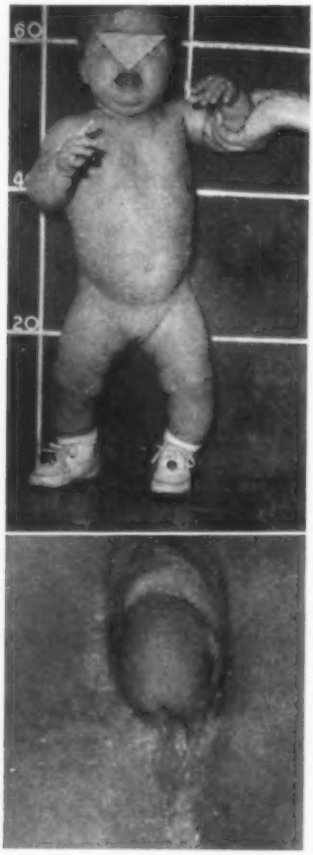

Fig. 1.—A. W., aged 10 months. Typical case of female pseudohermaphroditism. Patient considered a hypospadic male at birth.

Fig. 2.—D. H., aged 6 years. Demonstrating marked influence of excessive androgen for a prolonged period.

servation was made in four cases (C. B., A. W., B. W., and B. A.). In two of these cases (A. W. and B. W.) the correct sex reassignment was made within the first two weeks of life.

The size of the clitoris revealed progressive hypertrophy which was directly proportional to the length of time during which treatment was completely neglected or inadequate. The clitoris was partially covered by a prepuce and joined with the labia by two tough fibrous chordae. This usually resulted in a retraction of the clitoris toward a diminutive vaginal orifice. On the ventral aspect, as a rule, there was a furrow between the chordae extending from the tip of the glans to the base of the clitoris.

The labia were pigmented in two of the females and were fused to variable degrees in all cases, which resulted in outstanding anomalies of the introitus (Table I). In three cases there was a complete fusion of the labia. The cervix and urethra opened into a common cavity or urogenital sinus presenting an opening which resembled the orifice of a normal urethra situated in a dimple at the base of the clitoris. In two instances, A. W. and R. L. H., the urethral orifice opened into the anterior vaginal wall; in one case there was a normal female urethra but no vaginal orifice due to fusion of the labia.

The relationship of the internal genital organs was obtained as a result of either (a) surgical procedures, (b) endoscopy, (c) x-ray with a catheter in the urinary bladder at a time when radiopaque medium had been instilled into the vagina, (d) bimanual rectoabdominal palpation, or (e) at autopsy. The uterus and adnexa were consistently normal. It therefore became apparent that the process of virilization had begun after the eleventh or twelfth week of gestation, thus affecting only the clitoris and vulva which are derived from the fetal cloaca.[5]

In the cases of macrogenitosomia precox, the *male genitalia* presented variable degrees of abnormality. A case (R. R.) is illustrated in Fig. 3. This child presented a salt-losing syndrome at birth which persisted for approximately eighteen months and did not exhibit excessive virilization until 4½ years later.

Uniformly during the immediate newborn period, these males showed minimal clinical evidence of excessive androgenic secretion. In fact, the syndrome might have been overlooked in all of the males of this series had it not been for signs and symptoms associated with the salt-losing syndrome. The penis began to show evidence of abnormal growth as early as 2 months of age in one patient, J. B., and as late as 6 years in another, R. R. In the latter patient, the penis suddenly grew to adolescent size (Fig. 3) in a matter of six weeks, with the appearance of sparse pubic hair. The testes were small and soft at the time the patient was first seen by us at the age of 6 years and have remained so throughout our period of observation. One infant, J. B., possessed abnormally large testes at birth, which persisted up to 1 year of age. At this time, death occurred secondary to an upper respiratory infection, and, unfortunately, potent adrenal steroids were not available at that time. An autopsy showed aberrant adrenal tissue within the testes which accounted

for the unusual size of these organs. Aberrant adrenal tissue was also found in a case of macrogenitosomia precox of the salt-losing type reported by Wilkins, Fleischmann, and Howard.[6] The prostate was enlarged and comparable in size and consistency to that of an adolescent male.

Fig. 3.—R. R., aged 6 years. Typical case of macrogenitosomia precox in which definite evidence of virilization occurred late. Note large penis but paucity of pubic hair, and small testes.

The scrota were generally slightly hyperpigmented. This constituted, perhaps, the earliest sign of virilization in the males of this series. Rugae in the normal transverse position were somewhat exaggerated when compared to normal individuals of similar chronological age.

Anatomical findings common to males and females included early appearance of pubic hair, the presence of acneiform rash, and accelerated somatic and skeletal growth. The degree of these abnormalities was dependent upon the age of the patient and the duration of adequate control of androgen secretion by exogenous cortisol.

All of the males of this series showed advanced growth which placed them well above the upper percentiles for normal individuals of similar sex and chronological age. Likewise, two females, D. H. and K. S., exceeded the normal percentiles for height and weight. By the use of adequate steroid therapy, we have been able to control the precocious growth quite satisfactorily in the remaining cases.

Unfortunately, the patient illustrated in Fig. 2, D. H., did not receive adequate medical care and demonstrated the typical growth pattern of the cases seen prior to the current era of steroid therapy. This patient, during the first ten years of life, exceeded the normal rate of growth with an early closure of the epiphyses. She had completed her longitudinal growth and fell below the sixteen percentile level when plotted on the Iowa Growth Chart. Her sibling did not come to our attention for diagnosis and treatment until the age of 7 months, at which time her bone age was within

normal limits and has been so maintained with steroid therapy.

Serial bone maturation studies were made on seven additional cases, and it has been possible to control the tendency toward advanced bone age by adequate steroid therapy.

Precocious growth of pubic hair was noted in six cases (Table I). In all of these cases, it appeared after the neonatal period and was gradual in its progress. In four cases it was the first symptom noted by the parents and prompted them to seek medical advice. Two distinct patterns were observed in the development of this sign; one group of three patients—D. H., P. H., J. B.—began to show evidences of growth of hair at 6 months to 1 year of age, while the others showed such evidence of virilization at the age of from 2½ to 6 years.

Acne was observed as a persistent finding in one female, D. H., and in two of the males, R. R. and H. T. Its onset was at 3½, 5, and 6 years of age. Steroid therapy resulted in a cure in the female at a time when a good suppression of urinary 17-ketosteroids was evident.

Abnormality in the regulation of salt excretion occurred with high frequency in our series and was observed in ten of the fourteen cases. This abnormality was present in all of the males and in five of the ten females at the time of our first observations.

It is of interest that two of the males, R. R. and C. B., were temporary salt-losers over a period of eighteen and thirty-six months, respectively.

Characteristic of this complication of the adrenogenital syndrome is the abrupt and recurrent dehydration with shock and circulatory collapse which persisted in one patient, A. W., for twenty-one days before adequate treatment was started. Vomiting was a prominent symptom in all of these cases and became apparent usually at the time of initial feeding. Diarrhea was an inconstant finding. Renal losses of salt and water, which constitute an important aspect of this complex, were not accurately measured. Polyuria, which is difficult to evaluate in the newborn infant, was obvious in at least two cases and preceded diarrhea and vomiting. This was associated with a disturbance in plasma electrolytes.

The range of plasma electrolytes in five patients was as follows:

Sodium: 122-134 mEq./L.; normal range, 136-150 mEq./L.

Potassium: 6.8-10.4 mEq./L.; normal range, 3.6-5.6 mEq./L.

Bicarbonate: 12-19 mEq./L.; normal range, 19-29 mEq./L.

Chloride: 92-106 mEq./L.; normal range, 96-106 mEq./L.

Hypoglycemia was not established as a contributory factor in the symptomatology, and in three cases tested the fasting blood sugar was within normal range.

Additional laboratory data not necessarily associated with salt-losing syndrome or sex are listed here.

Urinary 17-ketosteroids 1.9-32.8 mg./24 hr.

Total eosinophils 60-1,277 per cubic millimeter.

Accelerated bone age +1 to +7 years (3 cases).

Chromosomal pattern; male in one case, female in five cases (one erroneous sex assignment).

The urinary 17-ketosteroids ranged between 1.9 and 32.8 mg. per 24 hours with the lowest value being obtained from a newborn infant and the highest value from D. H. who was not adequately treated until 10 years of age. Elevated values are pathognomonic of this syndrome, and, as stated previously, constitute a very important diagnostic and therapeutic aid. The total eosinophil counts ranged from 60 to 1,277 per cubic millimeter, and were definitely elevated in the cases with abnormality in the regulation of salt. In the latter, it ranged from 320 to 1,277 per cubic millimeter.

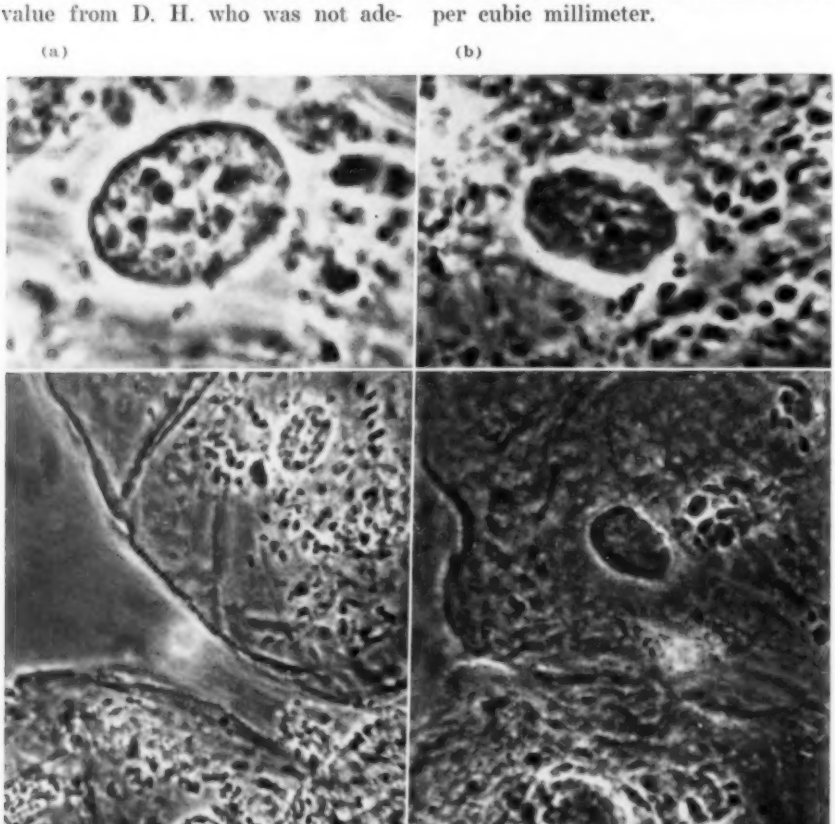

Fig. 4.—Phase contrast microphotographs, nuclei of fresh unstained buccal epithelial cells (upper, 45 × 1,000; lower, 7.5 × 1,000): (a) male with homogeneous distribution of chromatin; (b) female with one dark chromatin mass.

Recent techniques for determining chromosomal patterns of leukocytes and of squamous epithelium from buccal mucosa smears or from skin biopsies have been used in five cases of female pseudohermaphroditism in

which a female pattern was found and in one case of macrogenitosomia precox in which a male pattern was recognized. It was possible by study of chromosomal patterns to establish the female chromosomal sex in a patient erroneously assigned to the male sex because of a clitoris comparable in size to a normal penis.

With regard to technique, we have used the method of Moore and Barr.[7] Studies are currently being conducted by one of us (C. M.) in an effort to apply phase contrast microscopy to the study of nuclear chromatin in fresh cells. It appears that this method is accurate and eliminates artifacts due to staining and fixation. Its simplicity makes the procedure a useful one which may be especially suitable for screening purposes (Fig. 4).

Advanced bone age was demonstrated in C. B., although treatment was started early, and in two patients in whom treatment was delayed, D. H. and H. T. In the remainder, we were successful in controlling osseous growth. As stated previously, precocious osseous development resulted in an eventually short individual, as in the case of D. H., and may be partially or completely avoided with adequate therapy.

Routine intravenous pyelograms in four cases revealed no abnormalities.

Complete autopsies were performed in three of five patients who died. In one patient (R. L. H.) the adrenal glands were extremely large, with a combined weight of 19.9 grams. In another (J. B.) the glands were normal in size and microscopic examination revealed a hypertrophic zona reticularis. Examination of the testes in this case revealed enlargement, with islands of adrenal tissue scattered throughout the parenchyma. The prostate gland was also enlarged. In the third patient (B. W.), the size of the adrenals was within the upper limits of normal, weighing 5.8 grams, but on gross examination increased convolutions were observed. Microscopic examination showed a definitely hypertrophic cortex with no prominent zona reticularis.

A definite cause of death was established in only one case (B. W.) at autopsy, i.e., aspiration pneumonia. This introduces the likelihood of adrenal failure as a cause of death in four cases.

DISCUSSION

A comparison of this group of cases with those reported in the world literature by others reveals certain similarities and differences. The largest group of 67 cases was reported by Wilkins and associates.[8] Fifteen of their patients were of the "salt-losing" type, six of whom expired before the advent of cortisone therapy. Fifty-five patients were treated with cortisone. Five females were recorded as males and remained untreated.[5]

The sex ratio of our series compares with that of Grumbach[9, 10] and others. We agree that the sex distribution is influenced by a higher incidence of untreated males. In our series, as in Grumbach's, the sex ratio among siblings was near unity.

The familial incidence in our series is high, with six cases out of fourteen representing three pairs of siblings. In an additional case, B. A., there is a strong history of familial incidence

with an older sibling dying of neonatal vomiting. Each pair of siblings had identical clinical manifestations as follows: (a) two pairs of salt-losers; (b) one pair with virilization only and no evidence of adrenal cortical insufficiency. The size of the families in which familial incidence occurred was as follows: (a) two children with both (R. H. and R. L. H.) affected; (b) three children with two siblings (D. H. and P. H.) affected; (c) six children with two siblings (J. B. and C. B.) affected.

With respect to outcome, the following comments may be made:

The availability of cortisone therapy resulted in a sharp dividing line. Out of six salt-losers treated before the advent of cortisone, four expired "in crisis" after a survival time ranging from sixteen days to one year (Table I). H. T. was a mild temporary salt-loser with recurrent dehydration and failure to gain weight during the first five months of life. From this point no evidence of virilization was recognized until 3½ years of age, when signs of macrogenitosomia precox appeared and cortisol therapy was instituted. Another patient, R. R., as mentioned above, was also a temporary salt-loser and required DCA and salt therapy for eighteen months. It was not until the age of 6 years that the need for cortisol was recognized in order to control incipient virilization. This patient is currently doing well on steroid therapy.

Four salt-losers were observed after 1952 and received cortisone and, in addition, DCA and salt for variable periods; of this group, three are alive and well controlled, and one patient died of bronchial aspiration at the age of 1 month. The remainder of the cases with virilization alone which have come to our attention after 1952 are being well controlled with steroids. A possible exception is S. P.; this patient has moved to an unknown location and is mentioned later as a possible case of "freemartin" female pseudohermaphroditism.

Diagnosis.—Regardless of the clinical variant, the key to the diagnosis of virilizing adrenal hyperplasia resides in the demonstration of an excessive androgen secretion which results in an abnormally high urinary 17-ketosteroid output. The confirmatory test consists in the suppression of this secretion by cortisol administration.

There are several clinical states which suggest virilizing adrenal hyperplasia and in which laboratory studies may be resorted to in establishing the diagnosis:

1. *Excessive vomiting and dehydration in a newborn infant* should be considered with suspicion when no anatomic or infectious cause can be demonstrated.[11] The patient with virilizing adrenal hyperplasia is particularly prone to acidosis; there is polyuria with excessive excretion of sodium and chloride which requires large amounts of fluid and electrolytes to maintain a precarious balance. Examination of the genitalia and 24-hour urinary 17-ketosteroid determinations are the mandatory next steps when this symptomatology is manifest. Urinary collection may be considerably simplified by the adoption of plastic sheet "metabolic beds," which have proved very satisfactory in our experience.

2. *Anomalies of sex differentiation* in a newborn infant include hypospadism with cryptorchism or intersexuality and true hermaphroditism. Before the advent of reliable hormone assays, exploratory laparotomy and gonadal biopsy constituted the only reliable manner of accurately evaluating these patients. Whenever substantial evidence in favor of virilizing adrenal hyperplasia is present either in the form of clinical evidence of a salt-losing syndrome or of a high 17-ketosteroid output, a firm diagnosis of femininity can be advanced and the frequently erroneous assignment of sex rectified. Cytological studies are now available which accordingly confirm the existence of a female chromosomal sex pattern.[12, 13]

Two of our cases, however, will illustrate the unforeseen difficulties encountered in applying these principles:

C. B. was erroneously assigned to the male sex. This was not immediately recognized; furthermore, a urethrogram showed no urogenital sinus or vagina, and only a small diverticulum which was interpreted as being a prostatic utricle was observed. An "enlarged prostate" was believed to be felt at rectal examination. The parents thereupon firmly decided to rear the infant as a male and objected to any surgical exploratory procedure. Cystoscopy was not accepted nor a skin biopsy for cytological determination of sex. The patient is now 4 years old and has outgrown his salt-losing syndrome. "He" still has the appearance of an extreme cryptorchic hypospadiac male.

S. P. was first admitted at the age of 4 weeks and assigned a female. There were a phallus-like clitoris and coalescent labia with an external urinary orifice at the base of the clitoris; no introitus was present. There was no evidence of salt-losing syndrome and 17-ketosteroid output was 0.95 mg. per 24 hours. At the age of 22 months, the bone age was slightly advanced to 3 years, and 17-ketosteroid excretion was 1.9 mg. per 24 hours. Cytological sex pattern was unquestionably female. Urethrogram followed by endoscopy showed a urogenital sinus with a cervix and distal urethral opening. The decision at this point was to withhold cortisol and wait for signs of progressing virilism in the form of increasing 17-ketosteroid output and bone maturation.

In the event of a hormonal and osseous status quo this patient could be one of the very rare cases of "freemartin"* female pseudohermaphroditism, in which a masculinizing influence exerts its temporary action during the individual's fetal life. Examples include a maternal arrhenoblastoma of the ovary and exogenous androgen and progesterone administration.[14, 15]

3. Virilization in a female child should not be confused with functional states like hirsutism or precocious pubarche which can easily be eliminated because of their common familial character and normal 17-ketosteroid excretion. In Cushing's syndrome there are simultaneous symptoms of glucocorticoid involvement in the form of obesity, moonface, striae, hypertension, and osteoporosis.

Virilizing adrenal tumors occur postnatally and result in extremely high urinary 17-ketosteroid excretion. Virilizing tumors of the ovary are also rare. An adnexal mass is often perceptible. They rapidly cause extremely high amounts of androgen to appear in the urine, and this is of the

*When twinning occurs in the cow and the twins are of opposite sex, the androgens secreted by the male twin cause the female member of the pair to be born as a sterile intersex known as the freemartin.

beta isomere type. Neither of these conditions responds to cortisol administration.[16]

4. When confronted with *precocious virilization in a male child,* reasoning along similar lines eliminates true precocious puberty whether familial or due to intracranial processes with precocious release of pituitary gonadotropin in which 17-ketosteroids attain only adolescent levels. On the contrary, in virilizing adrenal hyperplasia, adult levels may be reached or exceeded. The highest 17-ketosteroid levels are encountered in Leydig cell tumors and adrenal virilizing tumors. In these cases the 17-ketosteroid levels are not depressed by cortisol therapy. Furthermore, these tumors are usually unilateral.[16]

Pathogenesis.—The secretion of adrenal cortical hormones is regulated by the elaboration of pituitary ACTH. The secretion of ACTH is in turn inhibited by a feed-back mechanism sensitive to any increase of blood hydrocortisone levels. The basic anomaly in virilizing adrenal hyperplasia is an enzyme deficiency in the organism resulting in the inability to convert 17-hydroxyprogesterone into hydrocortisone, thus stimulating ACTH secretion. The final result is a diversion of the normal steroid metabolism toward the production of androgenic steroids; their secretion in excessive amount exerts no inhibitory action on pituitary ACTH secretion.

Pregnanetriol is the characteristic final metabolite appearing in large amounts in the urine. The fact that the mean increment of pregnanetriol after ACTH administration is higher in the parents of affected individuals than in controls lends considerable weight to the hypothesis that virilizing adrenal hyperplasia is a genetically determined inborn error of the adrenocortical steroid metabolism.[17]

Some evidence points to the fact that impaired hydroxylation of C_{21} interferes with the synthesis of both hydrocortisone and desoxycorticosterone. An increased production of desoxycorticosterone is believed to account for the cases in which there is hypertension (five out of sixty-five in the Wilkins series).[18, 19]

Changes of the external genitalia are variable according to the fetal age at which the process of virilization starts. As far as can be ascertained, none of our patients presented a contradiction between their gonadal and chromosomal sex. Although differential diagnosis, distinguishing male pseudohermaphrodites and true hermaphrodites from female pseudohermaphrodites, may sometimes be difficult on purely morphological criteria, the female pseudohermaphrodites who develop as a consequence of fetal virilizing adrenal hyperplasia appear to be female from both gonadal and genetic standpoints.[20]

The effect of cortisone treatment on growth can readily be understood when its catabolic effect and the anabolic action of androgens are kept in mind.[21]

MANAGEMENT

The management of virilizing adrenal hyperplasia consists of medical, psychological, and surgical aspects.

The *medical management* is directed toward controlling (1) excessive androgen production in all cases, and (2) excessive salt loss when this feature of the abnormality is present.

1. Androgen excess is controlled by achieving physiological levels of body cortisol through administration of steroids. Physiological doses of cortisol must be administered to these patients for a lifetime and are without untoward effects. Thus the stimulus for ACTH production and subsequent excessive androgen formation is controlled. It is advocated that the intramuscular route be used initially and, if possible, continuously. However, we have been successful in controlling our patients with orally administered medication after early parenteral control. The recommended initial dose is large, and reduced after maximal suppression of urinary 17-ketosteroids is achieved (five to seven days) to minimal quantities which result in sustained suppression. The recommended *initial dose* of cortisol in infants is 25 mg. intramuscularly per 24 hours and 50 to 100 mg. intramuscularly per 24 hours in older children. A urinary 17-ketosteroid excretion of 1 mg. per 24 hours should be achieved in infants and 4 to 6 mg. per 24 hours in older children. The *maintenance dose* in infants is 10 mg. per 24 hours intramuscularly or 25 mg. every third day; in older children, 25 mg. daily or 75 mg. every third or fourth day. The exact dose must be individualized and is governed by the urinary 17-ketosteroid excretion. The maintenance dosage by the oral route of administration ranges from three to four times that of the intramuscular route in divided doses at six-hour intervals. According to Wilkins,[22] 5 mg. of prednisolone twice daily in older children may be adequate. The depot form of hydrocortisone has been used to a limited degree and may prove of value.

TABLE II

PATIENT	AGE RX BEGUN	CORTISOL DOSAGE PER DAY (MG.)	17-KS BEFORE TREATMENT (MG./24 HOURS)	17-KS AFTER TREATMENT (MG./24 HOURS)	REMARKS
D. H.	10 years	30 I.M.	32.8	5.1	
R. R.	6 years	50 P.O.	8.8	2.6	Virilized late—age 6 years
H. T.	4½ years	25 I.M.	8.5	2.4	Virilized late—age 4 years
K. S.	4½ years	75 P.O.	7.6	2.0	Delayed Rx—family not cooperative
C. B.	2 days	25 I.M.	6.7	0.7	
P. H.	7 months	30 P.O.	2.0	0.6	
A. W.	2 weeks	25 I.M.	5.4	0.2	
J. J.	1 week		7.0	1.0	Treatment begun by Dr. Wilkins; Rx: halogenated derivative

I.M. = Intramuscularly.
P.O. = Orally.

One of our cases, J. J., aged 1 year, was seen originally by Wilkins and constitutes one of his series which is being controlled by one of the halogenated derivatives of hydrocortisone. The initial ketosteroid levels and the suppression by steroid therapy in our cases are illustrated in Table II.

In cases of female pseudohermaphroditism that are being raised as females, there is a need for continuous

therapy. In cases where there is a misassignment of sex and the individual is being reared as a male, it is questionable whether steroid therapy should be instituted unless it is necessary to control osseous growth and permit near-normal longitudinal growth. It is obvious that steroid therapy of such a degree to permit menarche is highly undesirable in these cases from many points of view.

In cases of macrogenitosomia precox, it is desirable to suppress androgen production in order to control virilization and also to delay epiphyseal closure. Furthermore, suppression of androgen output by the adrenal cortex will result in the release of pituitary gonadotropin at puberty and thus influence gonadal maturation in either sex.

2. When *abnormal losses of salt* are associated with virilizing adrenal hyperplasia, daily sodium chloride intake must be increased by 3 to 5 grams in infants and 4 to 8 grams in older children in order to establish adequate balance. In addition, desoxycorticosterone (DCA) is frequently required. It is preferable to implant 125 mg. pellets in the subcutaneous tissues at nine- to twelve-month intervals. Gardner[19] states that long-acting DCA trimethyl acetate when administered intramuscularly at monthly intervals constitutes a highly satisfactory method of treatment.

In our experience, it has been possible to discontinue DCA therapy after 18 to 48 months, and also the salt intake has been reduced to a point that voluntary ingestion at mealtime is adequate as the child grows older. The reduction in salt requirement has been attributed to a compensatory increase of aldosterone in response to sodium loss subsequent to secretion of heretofore unisolated "sodium-losing substance."[23]

Adequate *psychological management* and *counseling* of parents and patients cannot be overemphasized.[24, 25] The main problems to be coped with are those related to precocity and uncertainty as to gender role. Extensive studies have shown IQ distribution among these children to follow the standard pattern. In spite of their often remarkable physical precocity, their mental development follows that of their chronological age. It is essential to point out this discrepancy to parents and teachers who tend to manage these children as they would a child of advanced maturity. Psychosexual development follows the chronological age, permitting the acquisition of adequate patterns of sexual behavior and socially acceptable restraint.

Surgical treatment has certain limited but precise indications, guided by some well-established principles.[26] Of these, the respect for the assigned sex should be axiomatic; spectacular "changes of sex" in patients old enough to have acquired a fixed gender role result in crippling psychological trauma.[24] Assignment of the eventual sex should be determined chiefly by the anatomical aspects of the external genitalia.

In the vast majority of cases, two simple procedures are resorted to:

1. *Clitoridectomy.*—This is always indicated if the clitoris is large enough to be conspicuous, as a hypertrophic clitoris often represents a source of embarrassment and is a possible cause

of lingering doubt as to the subject's femininity. With perfected techniques, only the cavernous portion of the organ may be removed, thereby conserving its erotic potential.

2. *Plastic Remodeling of the Urogenital Sinus.*—Usually consists of simple separation of the fused labia. In patient P. H., this was performed at the age of 7 months, with good results.

In contrast to intersexes, laparotomy with a view to exploring the internal genital organs is not justified in ascertained virilizing adrenal hyperplasia.

In a small number of extremely virilized patients, many of them dating from the pre-cortisone era and reared as boys, plastic procedures resulting in a closer simulation of male external genitalia may be indicated. They will be preferred over surgical feminization with its necessary extensive extirpation of erogenous areas and psychological repercussions of a change of assigned sex.

SUMMARY

A survey is made of fourteen cases of virilizing adrenal hyperplasia observed in the last ten years. The clinical and metabolic variability of the disease is emphasized. The diagnosis and management are discussed. Recent advances in the physiopathology of the disease are briefly reviewed.

The authors wish to express their appreciation to Mrs. June Ellis for her assistance in preparing this article.

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The probable reason that so many pediatricians are deans is that their clinical interests do not conflict with medicine, surgery and obstetrics, and their knowledge of child behavior helps their relationships with faculty and students.

From an editorial in the *Medical Bulletin of the Los Angeles Childrens Hospital* by Dr. W. C. Davison, Dean of Duke University School of Medicine.

LEARNING DISABILITIES ASSOCIATED WITH LESSER BRAIN DAMAGE

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RECENT studies of children diagnosed as "school problems" indicate that physicians, psychologists, and teachers are thinking in terms of organic deficit as a contributing factor in aberrant behavior.[1, 2]

In our study of cerebral palsy and other brain-damaged children over the past five years, observations have been made which help to elucidate some of the problems of children in whom the integrity of the nervous system has been interfered with either pre- or postnatally.

Our program has been described elsewhere.[3] In addition to a nursery school, there are an admission and follow-up clinic and an evaluation service for children with atypical development and aberrant behavior.

The children are observed in the nursery school setting by both the teacher and the psychologist. Psychological tests include the usual standardized intelligence and developmental scales. However, in most cases, special tests of perception, visual-motor coordination, auditory memory span, qualitative approach to tasks, and clinical observation are of greater significance in revealing areas of difficulty and disturbance. Frequently the variability and inconsistency of performance is a cue to areas of functioning that are then pursued more carefully. Often the test items and the method of administration must be adapted to the child, so there are no norms available or standardized comparisons that can be made. Research is being done to correlate various psychological tests with particular behavior and known brain damage. The following cases are illustrative.

Case 1.—S. B., a 7½-year-old boy, had been born prematurely on Aug. 8, 1951, weighing 4 pounds 14 ounces. It was the first pregnancy of the Rh-negative mother. There had been no increase in titer, but some bleeding had occurred during the first, second, and third months of pregnancy. Development was slow. He did not sit up until 10 months and walked at 22 months. A neurological examination revealed a mild spastic left hemiplegia, involving the arm more than the leg. X-rays of the skull and an electroencephalogram were noncontributory. Eye examinations have been normal. He was observed in our pre-nursery school program during the first 3 years and later entered a normal nursery school, and then public school. The parents have been very cooperative and there has been good communication between our activity and the other schools attended. The boy has had a Strayer operation on the affected leg and walks and runs within normal limits. He uses his left hand in playing ball, climbing, and other activities.

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Psychological testing done at 5 years of age reports the following:

"S. is functioning at average to high average level intellectually, and was able to score well within the average range of the Binet in spite of his motor handicap which caused difficulty on some test items. Comprehension was good and his understanding as well as his ability to express himself showed no psychological difficulty. S. was able to engage with me in pretend play involving abstract ideas and concepts. He has imagination and initiative commensurate with his age level. He does not appear to be overly concerned about his physical handicap and compensates well with his motor difficulties."

In nursery school it was noted that he had difficulty in drawing or painting and that at times he appeared confused when given oral instructions.

At 7½ years of age S. B. is in public school. He is a good reader and above average in mathematics. He has no speech difficulty, but he has had considerable trouble in two areas: writing and taking group instruction. Although there is no motor involvement of the right hand, writing and drawing is very difficult for him. The teacher also describes him as failing to grasp or understand instruction given to the group, even though he does well when these are given directly or individually to him. The home and school situations are better than average, yet his frustration and discouragement at these failures is noticeable. He undoubtedly will compensate for them as he matures.

CASE 2.—D. D., a 7½-year-old girl, was born July 14, 1951, at full term, weighing 7 pounds 2 ounces. A traumatic delivery resulting in a mild right hemiplegia involving the arm more than the leg. D. D. was an alert, active, charming little girl, minimally incapacitated by her handicap. She attended nursery school very irregularly, chiefly because the mother felt that her condition was so good that she should be in a normal nursery school. She returned to the follow-up clinic at irregular intervals and it was noted that her functioning as she became older was not as good as had been anticipated. It was felt that this was due to emotional problems in the home rather than to the child's inherent intelligence. The parents continued to be reluctant to accept the child as having any handicap. In a psychological test when she was 4 years of age, the examiner noted that the parents were exceedingly anxious about her. The father kept stressing all the things that D. did at home and how they taught her to be good, nice, etc. The psychologist noted that failures related particularly to deficiencies in background and upbringing. She did not attempt things which called for impetuousness and initiative because she seemed inhibited. The parents reacted to every failure with disappointment fear, and drilling of the child. The parents evaded getting psychological help always with the feeling that everything was normal and that she would function all right. When she started public school, the teacher complained because of hyperactivity and failure to pay attention to teachers' commands or orders. She was therefore retested at the age of 4½ with the following comment from the psychologist.

"D. D.'s performance on the Binet was well within the Dull Normal range. Analysis of sub-tests passed and failed showed that she passed all of the items at year three with a fairly regular progression of successes and failures to year five where she was unable to pass any of the items. Comprehension of verbal instruction was good, vocabulary was only slightly below her age level, but meaning and usage of verbal material was correct and appropriate. Immediate memory span and attention was poor, such as on repeating digits or sentences, which may be related to the distractibility and hyperactivity mentioned above. On the basis of the present intelligence tests, D. D. cannot be considered a seriously retarded

youngster and is probably capable of at least average intellectual ability. The difficulty she had with some of the items on the Binet, digits, drawing, etc., substantiates the history of brain damage."

Although presenting some signs of central impairment, the impression again was that most of her difficulties were of an emotional nature and resulted from conflict in the home and the child's relationship with her parents. Psychotherapy was discussed and the parents have finally consented to get help in the management of this child.

This child, with the double disadvantage of slight motor and perceptual difficulty and a great emotional factor, failed completely in public school and has been placed in the restricted environment of a school for the handicapped.

CASE 3.—S. S., a 6-year-old girl, was born Feb. 8, 1952, at full term. Labor was difficult. The baby failed to cry spontaneously at birth and was placed in oxygen. She was a slow starter and had some feeding difficulties. She had a mild left hemiplegia. Her IQ when she entered the prenursery school was 105. Electroencephalogram and skull x-rays were noncontributory. S. S. is a blond, vivacious talkative, attractive child. Upon leaving our program and the city, she was placed in a normal nursery school and later kindergarten. After a year in the kindergarten-primary class, the mother returned to our follow-up clinic because the teacher had suggested that S. S. repeat the kindergarten-primary class rather than attempt a more advanced one. The following is a quotation from the teacher's report.

"Her speech is clear, she tells imaginative stories, she is aware of numbers and is beginning to understand the sequence. She seldom sings with the group but does enjoy rhythm. Because of her physical involvement and immaturity she is very slow in developing skills and familiarity with the use of art materials. With prompting she will share and cooperate in group activities. She will not complete even the most simple coloring exercise unless she is constantly encouraged to do so. She enjoys standing about the room with nothing apparently in mind as to activity. When encouraged, she will string beads, work with clay or a puzzle and play in the playhouse for a short period of time. She is gradually improving in her work and play habits."

This description by an observant nursery school teacher is characteristic of the child with a neurological deficit.

CASE 4.—K. L., a girl, was born Oct. 26, 1952, after a difficult delivery with x-ray evidence of a linear skull fracture. She was admitted from another hospital because of convulsions shortly after birth. This child was seen infrequently because of residence in another city. She had no more convulsions but it was evident early that she had a right hemiplegia. She is an attractive, alert, talkative child with a good family background. She was placed in a normal nursery school in her home town. On follow-up at our clinic, the mother reports that she has difficulty in writing and drawing. The teacher also describes her as inattentive and unable to grasp directions given to the group.

CASE 5.—W. K., a boy, was born prematurely July 6, 1951, by breech extraction and weighed 3 pounds 14 ounces. His development was slow. He came to us under 2 years of age with a diagnosis of spastic paraplegia. Intelligence quotient was 104. W. K. is a charming, verbal child, with a keen sence of humor who enjoyed nursery school. The teacher noted his tendency to evade and circumvent certain tasks which presented problems to him, such as drawing, and it was anticipated that he would have learning difficulties when reaching school age. He went from our activity to the school for the handicapped. Our predictions proved correct and W. K. had a repeat psychological test when 6 years of age. Although well within the range of

average intelligence, he had difficulty in writing and in the arts. He also frequently "blocked" when required to make quick shifts in attention. At times there was difficulty in starting speech. He is being retained in the school for the handicapped even though the extent of the motor involvement is not such as to necessitate this. In the situation of a large classroom of normal children, the above deficiencies would interfere with his work enough to prevent his progressing at the rate he is capable of in a more sheltered situation. With guidance he should be able to compensate for these perceptive and mild aphasic handicaps as he matures.

The story of two brothers will be briefly reported to illustrate the merging of the above type of brain-damaged child with the one who has no demonstrable motor involvement but mere perceptual difficulties.

J. F., a boy, was born prematurely Aug. 14, 1950, weighing 2 pounds 2 ounces. He progressed satisfactorily in spite of his prematurity for the first 52 days. At that time he had a cyanotic episode accompanied by fever of 38.2° C. Subsequent to this episode the nurse noted that his right arm did not move as well as the left and that his leg activity was diminished. This episode in the nursery has been previously described.[4] Follow-up on this boy by pediatricians and orthopedists places his handicap in the lower motor neuron class. On May 10, 1956, at the age of 5 years, and 7 months, a psychological test was done and the following note made.

"His gross intellectual functioning is definitely at a Superior level. This is evidenced not only on the Stanford Binet, where he passes all the tests at the year five and has a regular progression of failures through year ten where he is able to pass one sub-test, but also in his projective drawing and general approach to problem situations. There is no evidence of central damage that interferes with intellectual functioning. I found no perceptual difficulties, associated difficulties or memory defect."

It is interesting and pertinent that this comment by the psychologist was made under the misapprehension that he was dealing with a cerebral palsy motor-handicapped child.

An older brother of J. F. was also born prematurely in 1942. Although his birth weight was 5 pounds 7 ounces, he was a difficult feeder and as late as three months it was noted that he still appeared premature. No particular findings are noted thereafter until he started school. It was then found that he had difficulties in class. He had his first psychological test at the age of 7 years and has had two subsequent ones. On the last one at 14 years of age the following comment was made.

"There is a tremendous difference between his verbal scale ability and his results on the performance scale. For this reason it is not too meaningful to place him at a certain level although his verbal abilities are certainly well within the average range. He has difficulty with the block design test, object assembly and picture completion to such an extent that the question of organic involvement of some type is certainly raised. On the Weigl-Goldstein-Scheerer, the quality and level of his performance is also indicative of some organic involvement resulting in perceptual difficulties as well as poor visual motor coordination. I am certain that this is why he has difficulty with his handwriting. He handles emotionally stimulating material fairly well and is realistically oriented. The Rorschach reveals a fairly well integrated personality structure considering the probable handicap he must adjust to."

These boys come from an intelligent family where everything has been done to enhance their development.

DISCUSSION

Any interference with the integrity of the central nervous system should

make one suspicious of possible interference with normal intellectual functioning at some stage of development. The ordinary tests such as a neurological examination, electroencephalogram, and pneumoencephalogram are not sensitive enough to pick up these aberrations. Careful psychological, educational, and developmental tests are indicated, and, when these are done by skilled personnel, variations from the normal in the perceptual areas can then be detected, thus anticipating future learning disabilities. The most easily recognized disturbances are in the field of speech and hearing problems. In the larger communities at least, these two defects are usually detected and dealt with when the child enters school. The more subtle defects encountered are (1) expressive speech, (2) understanding oral commands, (3) writing, (4) subtle or perceptual disturbances in hearing, (5) memory, (6) control of hyperactivity, and (7) emotional control.

These children may have less motor disability, for instance, than a child with poliomyelitis or even a fractured arm, and yet they cannot be compared with these when a choice of school situations is contemplated. These children are fairly easily recognized once this syndrome becomes familiar to the physician, psychologist, and educator. The importance of recognizing this problem should be apparent. These children have good potential if they are helped to compensate for their deficiencies. On the other hand, they quickly become behavior problems unless the basic pathology is understood. The evaluation and the habilitation is the joint responsibility of medicine, psychiatry, and education. The last two cases illustrate the difference between the lower motor neuron handicapped child and the cerebral damaged child in the same family and very much the same environment. It also points out that the cerebral damaged child with minimal motor involvement merges with the one who has practically no demonstrable motor involvement and is therefore missed in the cerebral palsy group.

SUMMARY

In an habilitation program for brain-damaged children it has been found that children with little motor involvement merge with children who have no demonstrable motor handicap in presenting perceptual difficulty in areas of speech, hearing, writing, reading, memory, understanding, obeying oral commands, and in the control of activity. When not understood and dealt with properly, these deficits interfere with intellectual accomplishments. They cause emotional maladjustment and disturbance in socialization.

This group is salvageable and deserve the combined efforts of physicians, psychiatrists, and educators as well as the ancillary discipline to help them attain their optimum development.

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GROUP DYNAMICS IN THE TREATMENT OF EPILEPSY

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INTRODUCTION

THE use of group therapy as adjunct treatment in the care of patients with various diseases has been shown to be of great value to the practicing physician. Over twenty years ago, Schilder[1] first used this form of therapy on psychoneurotic patients; more than ten years ago, Amster[2] pioneered in applying this technique to the treatment of children with behavior problems. Milman[3] has reported on the value of group therapy with the parents of physically disabled children, and de Fries and Browder[4] have tried group dynamics with epileptic children and their mothers. Whereas the latter article deals with the treatment of epileptics in a large medical center where a battery of highly trained specialists—pediatricians, neurologists, psychiatrists, psychologists, and social workers—can be utilized, this is not always practical for the myriads of epileptics who live away from large medical centers. For the past two years we have attempted to modify this mode of treatment into an efficient and useful technique that can be applied to the office practice of any group of physicians. We wish to report our evaluation of this form of management.

Of all the "scare words" in medicine (i.e., cancer, heart murmur, polio), probably none causes more immediate anxiety to parents than epilepsy. We are approaching an era when laymen often know almost as much as physicians do about such diseases as multiple sclerosis and muscular dystrophy, through organized drives and educational programs; yet the average person's knowledge of epilepsy remains steeped in ignorance and superstition. Many parents, oftentimes well-educated and upper-income people, have confessed that they supposed epileptics gradually had more and more seizures, became more deteriorated, and eventually ended their days hopelessly retarded in m e n t a l institutions. A registered nurse remarked that her child had two seizures one evening because there was a full moon that night. We have cajoled, pleaded, and virtually forced parents to join our seizure clinic, parents so ashamed of the stigma that they chose to refuse medical treatment rather than be found attending a "fit clinic."

Parents can become so filled with remorse or so alarmed at the seizures that they lose all disciplinary control.

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The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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A typical example of this faulty approach occurred in a 14-year-old girl whose harried parents brought her to the clinic because she was rapidly becoming a juvenile delinquent. History showed that this girl's seizures began in early childhood; she had been managed excellently—drug-wise—and at the time we saw her had been seizure-free for ten years and off medication for four years. The parents had lived under the misapprehension that punishment would bring on a seizure, and actually had felt that her near-criminal antics could be accounted for by her epilepsy. Fortunately, they were able to accept the idea that they had a lot of "woodshedding" to catch up on. They instigated "treatment" and the child soon became a normal teen-ager.

We found that doctor-parent talks and pamphlets were only partially effective in clearing up a lifetime of superstition and ignorance. It was felt that if parents of epileptics could meet together and discuss common problems and fears and share individual successes, more lasting benefits could be achieved.

METHOD

The pediatric seizure clinic meets once a month; approximately twenty patients are enrolled. Each new patient receives a complete medical history, physical examination, and a diagnostic work-up that consists minimally of skull films, electroencephalograms (in children over 1 year of age), blood calcium, phosphorus, alkaline phosphatase, fasting blood sugar, and nonprotein nitrogen tests.

Prior to attending the clinic, the parents are interviewed by the social worker, who explains the group meeting and tries to clarify any misgivings or misconceptions the parents may have about epilepsy. She usually obtains additional family data which will lead to a better understanding of individual problems. The healthy sibling who is ashamed to bring his friends home because of the epileptic, or a timid schoolteacher afraid to have the child in her class, are examples of very real problems in many households. Usually this preliminary discussion with the social worker eases anxiety so that the newcomers to the group fit in more easily.

Both parents as well as the child are encouraged to attend each clinic session. During the first hour, the children remain in the nursery or waiting room, and the parents meet as a group with the doctors and social worker. The second hour is spent with the children.

During the discussion hour, the parents are encouraged to bring out any question or problems which have arisen since the previous session. Purely medical questions are answered by the moderating physicians; all others are bandied about by the group. Frequently parents who have coped with seizures for five or ten years have worked out solutions which are helpful not only to the novice but to the physicians as well. No one knows as much about rearing an epileptic, we feel, as the parent of an epileptic. When a parent informs the group that his child who has been having frequent seizures for years has gone a full month without one, less fortunate parents take heart. When the parents of a 3-year-old epileptic see and hear a teen-age epileptic tell of playing football

and dating, they realize—far better than books or doctors' lectures can show them—how optimistic they can be. This frees them of many of their anxieties and makes them better able to raise normal, well-adjusted children.

Since our clinic is in its second year and many oldtimers are now well aware of the pitfalls, fears, and misconceptions associated with epilepsy, they quickly "pounce" on newcomers and straighten them out with group action and consent. Committees are formed to find out such things as the driver's license requirements for this state, and which colleges will accept epileptics. They report their findings to the group.

One teen-ager, severely maladjusted by his seizures, was "adopted" by another, a boy about his own age whose seizures were much less severe and who was leading a well-rounded life. The two became close friends and gradually the maladjusted boy became motivated to enter into teen-age activities, even to the extent of dating, of which he had always been fearful. Interestingly enough, his seizures, which had occurred several times a day, have dropped off drastically and he has now been seizure-free for over two months. The group maintains a lively interest in this boy's progress.

In order to disseminate information on a once-taboo subject, the group invited all teachers, neighbors, and friends to an open meeting during which a movie on epilepsy was shown and questions answered. Approximately 150 attended.

Each of these examples represents a group effort by a band of parents troubled with a similar affliction and receiving instruction and reassurance through joint action.

The second hour of our seizure clinic is spent in seeing each child and his parents individually and rapidly, just long enough to hear pertinent comments, adjust medications, and refill prescriptions. The two hours spent in the clinic represents about the same amount of time it would take to see the same number of patients individually.

RESULTS

The value of this approach does not lend itself to statistical analysis. All of our patients are not well controlled, nor are they all neurologically normal nor of normal intelligence; yet each parent, we believe, has gained immeasurably in learning about his child's problems, and how to cope with them. The enthusiasm and gratitude of the parents make us feel that this type of seizure clinic fills a need and is most worth while.

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THE BACTERIOLOGICAL DIAGNOSIS OF CHILDHOOD TUBERCULOSIS USING BONE MARROW AND PERIPHERAL BLOOD ASPIRATES

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A NUMBER of authors have written enthusiastically of the results they have obtained using bone marrow aspirates in the diagnosis of infectious disease. The possibility of using bone marrow cultures in the routine diagnosis of typhoid fever has been considered by many investigators. Sacks and Hachtel,[26] in discussing the diagnosis of typhoid fever, stated the earliest report of the bacteriological culture of bone marrow biopsy material in the diagnosis of the disease is contained in a paper written by Gerbasi in 1925. Sacks and Hachtel were favorably impressed with the results they obtained with sternal marrow in the diagnosis of typhoid fever, and suggested the extension of the technique to the diagnosis of other types of infection associated at one time or another with a bacteremia.

Even though the adoption of the technique of bone marrow culture in the diagnosis of tuberculosis has been slow, the application of the principle has been logical since many authors have written of the similarity between the clinical entities typhoid fever and miliary tuberculosis. Debre and coworkers,[7] in 1936, were the first to study bone marrow cultures in the diagnosis of tuberculosis in children, according to Choremis and Danelatou.[5]

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The interest in the use of bone marrow specimens in the diagnosis of tuberculosis waned for a time, and it was not until the middle 1940's that articles on the subject appeared in any great number. Myers,[22] in the editorial, "Dramatic Advances on the Tuberculosis Front," praised Dr. Emil M. Schleicher for his valuable contributions in the field of laboratory diagnosis. As pointed out by Myers, 50 per cent or more of the diagnoses of generalized miliary tuberculosis in the past have been possible only at postmortem. With the advent of the antituberculosis agents it has become imperative that an early diagnosis be established if these drugs are to be effective. Schleicher[27] described his method of sternal aspiration and sectioning of gross sternal marrow units, thereby establishing the diagnosis of miliary tuberculosis before the appearance of the telltale signs, x-ray findings, and other procedures designed to detect the disease.

The belief that antemortem diagnosis of generalized miliary tuberculosis might be achieved by means of bone marrow sections was strengthened by the work of Chapman and Whorton.[1] In recent years a number of articles have appeared in the literature on the use of bone marrow in the diagnosis of infectious disease, especially tuberculosis. Gellis,[14] in editing

The Year Book of Pediatrics of 1954-1955, wrote the following comment on the article by Choremis and Danelatou[5]; "We have had no experience with bone marrow cultures in tuberculosis but are in agreement with the authors' recommendation that such cultures be made not only in tuberculosis but in other infectious diseases as well. This procedure deserves more attention than it has received in the past."

The literature on the subject of tuberculous bacillemia is too voluminous to be reviewed in this article. According to medical history, it was Weischelbaum in 1884 who first described the presence of acid-fast bacilli in the blood of tuberculous patients, Villemin, in 1868, having demonstrated by animal inoculation the presence of virulent tubercle bacilli in the blood of patients suffering from the disease. Beginning with the work of Villemin, Wilson,[31] in 1933, reviewed the subject of tuberculous bacillemia and, despite the fact that the references numbered in the hundreds, he remarked that the review was by no means exhaustive.

No lengthy discussion of the bacteriological study of tuberculous bacillemia has appeared in the literature since Wilson published his paper. With the revival of interest in bone marrow culture and the development of the newer concept of the pathogenesis of tuberculosis, a number of investigators have included blood culture technique in their studies.

TECHNIQUES

I. *Bone Marrow Examination.*—

The technique employed was essentially that described by Katz and Lifschutz.[16]

A. *Aspiration and Concentration.*—Following the suggestion of Katz and Lifschutz, the site of the aspiration was the upper end of the tibia in patients under 2 years of age and the iliac crest of all other patients. The concentration method using Hanks's solution was followed closely, and the sediment resulting from the centrifugation was used in making smears and cultures and for guinea pig inoculation.

B. *Bacteriological Study.*—(a) *Direct smears of sediment:* Three smears were made of the sediment of each specimen and stained by Ziehl-Neelsen's method.

(b) *Cultures:* Two tubes of modified Lowenstein-Jensen's medium (purchased from Difco Company) were heavily inoculated with the sediment. Tubes showing no growth were discarded at the end of the 60-day incubation period. Guinea pigs were injected with a transplant of the positive cultures in an attempt to establish the identity of the acid-fast organisms isolated.

(c) *Animal inoculation:* The sediment remaining, after cultures and smears were made, was then mixed with a small amount of sterile 60-mesh alundum and enough saline to make a suspension. The mixture was then thoroughly ground with a sterile pestle and 1 c.c. injected subcutaneously into the inguinal region of a guinea pig that had been found nonreactive to tuberculin. At the end of the 6-week period, a surviving animal was tuberculin tested and, if a positive reactor, it was sacrificed. The nonreacting animals were permitted to live another month and then sacrificed. At postmortem, the site of inoculation and

viscera were examined grossly for the evidence of tuberculosis and material for acid-fast stains and cultures was taken from the lesions.

II. *Blood Examination.*—

A. *Aspiration and Concentration.*—Five cubic centimeters of peripheral blood was added to a centrifuge tube containing 3 c.c. of sterile 10 per cent sodium citrate solution and the tube agitated to ensure thorough mixing. To this mixture was then added 30 c.c. of sterile 3 per cent acetic acid in triple-distilled water. The tube was centrifuged at 2,000 r. p. m. for 30 minutes. The supernatant fluid was carefully removed and 30 c.c. of sterile triple-distilled water was added to the sediment. The tube was then centrifuged at 2,000 r. p. m. for 15 minutes and the supernatant fluid discarded. The grayish sediment that remained in the bottom of the tube was used in making smears and cultures, and for animal inoculation.

B. *Bacteriological Study.*—(a) *Direct smears of sediment:* The method described for the preparation and study of bone marrow specimens was employed in the study of the blood specimens.

(b) *Cultures:* The cultures were handled in the manner described for the bone marrow specimens and animal inoculation was used for confirmation.

(c) *Animal inoculation:* Guinea pig inoculation was not routinely employed but, in the few cases, where this procedure was done, the method outlined for the bone marrow specimens was followed.

III. *Precautions.*—

In the preparation of the blood and bone marow specimens, great care was taken to avoid errors in technique that would lead to an erroneous conclusion. Thought was given not only to the preparation of the glassware and reagents, but also to the preparation of the slides and their subsequent microscopic study.

RESULTS

At the time the bone marrow and blood specimens were aspirated, the diagnosis was not established for any one of the patients considered in this study, but tuberculosis was a provisional diagnosis in every case. For the purpose of interpreting the results of this investigation, the 30 patients studied are categorized into three groups according to the definitive diagnosis and the factual data of each patient are recorded in the accompanying tables. Series I is composed of 13 patients who had a definitive diagnosis of tuberculosis without accompanying tuberculous meningitis. Series II is composed of 11 patients for whom the diagnosis of tuberculous meningitis had been established. The 6 members of Series III are patients who did not have a final diagnosis of tuberculosis.

Series I.—

Bone marrow study: Smears of the concentrated bone marrow specimens were positive for acid-fast bacilli in 5 of the 13 patients of this series, and 2 of the 5 were positive for *Mycobacterium tuberculosis* by both cultural methods and animal inoculation. Animal inoculation was done in 10 of the 13 cases, having been omitted in only 1 case in which the bone marrow smears revealed acid-fast rods.

Blood study: Smears of the concentrated blood were positive for acid-fast rods in 7 of the 13 cases. *Myco.*

TABLE I. SERIES I—TUBERCULOUS

NAME	AGE	SEX	RACE	FINAL DIAGNOSIS	KNOWN EXPOSURE TO TB	TUBERCULIN TEST	HISTOPLASMIN TEST	DURATION OF SYMPTOMS PRIOR TO ASPIRATIONS	TB THERAPY PRIOR TO ASPIRATIONS
J. H.	17 mo.	M	W	Miliary tuberculosis	Yes	Neg.*	Neg.	10 wk.	None
J. W.	9 yr.	F	N	Tuberculosis of lung, childhood type	Yes	Pos.	Pos.	4 wk.	None
J. S.	10 yr.	M	N	Tuberculous peritonitis	Yes	Neg.†	Neg.	6 wk.	None
G. G.	7 mo.	M	W	Pulmonary tuberculosis	Yes	Pos.	Neg.	5 da.	None
D. R.	11 yr.	F	W	Tuberculosis of lung, childhood type	No	Pos.	Neg.	4 wk.‡	None
R. S.	6 yr.	M	N	Pulmonary tuberculosis	Yes	Pos.	Neg.	3 wk.§	None
D. M.	18 mo.	M	N	Tuberculosis of long bones, hand and head	No	Pos.	Neg.	10 wk.	18 da.
K. B.	2 yr.	F	W	Tuberculous lymphadenitis	Yes	Pos.		8 wk.‖	None
G. C.	22 mo.	F	W	Tuberculosis of lung, childhood type	No	Pos.	Neg.	3 wk.	None
R. D. S.	6 mo.	M	W	Tuberculous bronchopneumonia and mediastinal lymphadenitis	Yes	Pos.	Neg.	11 da.	None¶
D. B.	5 mo.	F	N	Tuberculosis, childhood type	No	Equiv.	Neg.	2 wk.	None
K. A.	3 yr.	F	W	Cerebral spastic, infantile paralysis Inactive TB, childhood type	No	Pos.	Neg.	9 wk.	None
C. S.	5 mo.	F	W	Tuberculosis of lung, childhood type	Yes	Pos.	Neg.	12 wk.	4 da.

*Became reactive between fourteenth and twenty-first week of illness.
†Equivocal reading after ten weeks of illness.
‡Exacerbation of a 3-year infection.
§Exacerbation of a 5-year infection.

tuberculosis was isolated from 2 of the 7 cases with positive smears. One case gave positive results by smear and culture of both the blood and bone marrow specimens. The blood and bone marrow specimens from this patient also produced tuberculosis in the inoculated guinea pig, it having been the only blood specimen of Series I that was introduced into an animal. Three of the patients with negative bone marrow smears and cultures revealed the presence of acid-fast rods in the blood smears, and of the 3, *Myco. tuberculosis* was isolated from the blood of 1.

PATIENTS WITHOUT MENINGITIS

ROENTGENOGRAPHY OF LUNG	EXAMINATION FOR ACID-FAST BACILLI									REMARKS
	BONE MARROW			BLOOD			SPINAL FLUID		GASTRIC WASHINGS	
	SMEAR	CULTURE	ANIMAL INOC.	SMEAR	CULTURE	ANIMAL INOC.	SMEAR	CULTURE	CULTURE	
Fine miliary deposits bilat.	+	+	+	+	+	+			-#	
Suggestive healed primary infection, ? minimal activity	+	+	+	+	-				-	
Calcified healed primary complex	-	-	-	+	-				-	Liver biopsy at laparotomy, tuberculosis
Hilar lymphadenopathy, infil. apex, primary tuberculosis	+	-		+	-		-	-	-	
Collapsed middle rt. lobe, hilar calcification, primary TB, ? quiescent	-	-		+	+		-	-	-	
Collapsed middle rt. lobe with enlarged hilar nodes, probably tuberculosis	-	-		-	-				+	
Normal chest	-	-	-	-	-				-	Tubercle bacilli isolated from abscess
Infiltration rt. base	-	-	-	+	-				-	Lymph node biopsy, tuberculosis
Primary complex with hilar lymphadenopathy	-	-	-	-	-		-	-	+	
Bronchopneumonia with infiltration rt. upper lobe	+	-	-	+	-		-	-	-	Died 10 days after aspiration of specimens, autopsy performed
Soft infiltration rt. lung suggesting acute infection	+	-	-	-	-				-	
Dissem. pul. disease as TB, massive calcification rt. hilar nodes	-	-	-	-	-				-	
Hilar lymphadenopathy, pleural effusion	-	-	-	-	-		-	-		

‖Recurrence of a suppurative lymphadenitis quiescent for 12 months.
¶Terramycin had been given intravenously for 5 days prior to the aspiration of the specimens.
#Acid-fast organisms isolated from a specimen of a later date.

Series II.—

Bone marrow study: Smears of the concentrated bone marrow specimens were positive for acid-fast rods in 8 of the 11 patients of this series, and 5 of the 8 were positive for *Myco. tuberculosis* by both cultural methods and animal inoculation. Animal inoculation was done in 10 of the 11 cases, having been omitted in only 1 case in which the bone marrow smears revealed acid-fast bacilli.

Blood study: Smears of the concentrated blood were positive for acid-fast rods in 5 of the 8 patients for whom the bone marrow smears were positive,

TABLE II. STUDIES II

NAME	AGE	SEX	RACE	FINAL DIAGNOSIS	KNOWN EXPOSURE TO TB	TUBERCULIN TEST	HISTOPLASMIN TEST	DURATION OF SYMPTOMS PRIOR TO ASPIRATIONS*	TB THERAPY PRIOR TO ASPIRATIONS
S. B.	3 yr.	F	W	Tuberculous meningitis, miliary TB, tuberculous hip	Yes	Pos.	Neg.	2 da.†	Not for 10 wks.
M. C.	8 mo.	M	W	Tuberculous meningitis, miliary TB, pul. TB, primary	No	Pos.	Neg.	4 mo.	None
F. S.	4 yr.	M	W	Tuberculous meningitis, miliary TB, pulmonary TB	Yes	Pos.		4 wk.	8 da.
J. C.	8 mo.	M	W	Tuberculous meningitis, miliary TB, far advan. pul. TB	Yes	‡	‡	4 mo.	4 wk.
M. S.	4 yr.	M	W	Tuberculous meningitis, probable tuberculoma	Yes	Pos.	Neg.	3 wk.	5 da.
R. M.	2 yr.	M	W	Tuberculous meningitis, miliary TB	Yes	Pos.	Neg.	3 wk.	6 da.
R. E. M.	2 yr.	F	W	Tuberculous meningitis	No	Equiv.	Neg.	1 wk.	None
J. R.	17 mo.	M	W	Tuberculous meningitis, miliary TB	Yes	Pos.	Neg.	4 wk.	1 wk.
W. A.	3 yr.	M	N	Tuberculous meningitis, miliary TB, active pul. TB	Yes	Pos.		8 wk.	None
R. M.	9 mo.	M	W	Tuberculous meningitis, miliary TB, pulmonary TB	Yes	Pos.	Neg.	12 da.	None
L. O.	3 yr.	M	N	Tuberculous meningitis	Yes	Neg.§	Neg.	28 da.	17 da.

*Symptoms not necessarily those of CNS disease.
†Tuberculous hip for one year.
‡Results not recorded.
§Tuberculin test repeated seventeen days later was positive.

TUBERCULOUS MENINGITIS PATIENTS

ELECTROENCEPHALOGRAPHY	ROENTGENOGRAPHY OF LUNG	EXAMINATION FOR ACID-FAST BACILLI								REMARKS
		BONE MARROW			BLOOD		SPINAL FLUID		GASTRIC WASHINGS	
		SMEAR	CULTURE	ANIMAL INOC.	SMEAR	CULTURE	SMEAR	CULTURE	CULTURE	
Diffuse encephalopathy, suspect TB meningitis	Few areas calcification, particularly left chest	+	+	+	+	−	+	+	−	
Diffuse encephalopathy, suspect TB meningitis	Infiltration rt. upper lobe with miliary densities in remaining lung fields	+	+	+	+	−	−	+	−	No CNS signs at time of admission
Mod. severe diffuse encephalopathy, suspect TB meningitis	Miliary infiltration throughout entire chest	+	+	+	−	−	+	+	−	
	Miliary densities entire lung fields, cavitation and miliary dissemination	−	−	−	−	−	−	+	−	Admitted as terminal TB meningitis; died 4 days after admission
Diffuse encephalopathy, suspect TB meningitis, focalization on left	Interpreted as normal chest‖	−	−	−	−	−	−	−	−	Typical acid-fast organisms were not seen or cultured
Diffuse encephalopathy, suggestive TB meningitis	Disseminated miliary densities throughout entire chest	+	−	−	−	−	−	−¶	−	Relapsed after 7 months' antituberculosis therapy
Diffuse encephalopathy, suggestive TB meningitis	Sl. enlargement sup. portion rt. hilum with min. pleural thickening rt. base	+	−	−#	−	−	−	−	−	
Diffuse encephalopathy, suspect TB meningitis	Miliary densities throughout both lung fields	+	−		+	−	+	−	‡	
Diffuse encephalopathy, suspect TB meningitis	Diffuse nodular infilt. left lung field, consolidation rt. side, cavitation rt.	+	+	+	+	−	+	+	−	Incorrectly diagnosed as polio on admission 1 mo. before; died 32nd day this admission
Diffuse mod. severe encephalopathy, suggestive TB meningitis	Miliary infilt. throughout both lung fields	+	+	+	+	−	+	+		
Diffuse encephalopathy, suspect TB meningitis	No pulmonary abnormalities	−	−	−	−	−	−	−	−	

‖Film taken two months later interpreted as miliary infiltrate entire chest.
¶Acid-fast organisms isolated on admission seven months later.
#Animal died three days after inoculation.

TABLE III. SERIES III

NAME	AGE	SEX	RACE	FINAL DIAGNOSIS	KNOWN EXPOSURE TO TB	TUBERCULIN TEST	HISTOPLASMIN TEST	DURATION OF SYMPTOMS PRIOR TO ASPIRATIONS	TB THERAPY PRIOR TO ASPIRATIONS
E. H.	13 mo.	M	W	Iron deficiency anemia	Yes	Neg.	Neg.	5 wk.	None
V. M. W.	9 yr.	F	N	Acute meningitis, organism unknown	No	Pos.	Pos.	7 da.*	None
B. K.	4 yr.	F	W	Bronchopneumonia, pulmonary infiltrate Etiology undetermined	No	Neg.	Neg.	14 da.	12 da.
D. H.	5 mo.	F	W	Disseminated histoplasmosis	No	Neg.	Neg.†	4 wk.	None
T. M.	3 wk.	F	W	Subdural hygroma due to birth injury	Yes	Neg.	Neg.	2 wk.	None
R. W.	13 yr.	M	N	Diagnosis undetermined, acute lymphadenitis, generalized lymphadenopathy of undetermined etiology	No	Neg.	Neg.	6 da.	None

*Relapse of seven days after acute illness of three weeks before.
†Histoplasmin test positive when patient retested three weeks later.
‡CSF cytology and chemistry suggested a bacterial meningitis but no organisms isolated. All virus studies were negative. No mycological forms were seen or cultivated.

but *Myco. tuberculosis* was not isolated from the concentrated blood of any patient in Series II. Animals were not injected with the concentrated specimens from patients in this group.

Series III.—

Bone marrow study: Acid-fast organisms were not seen in the smears of the concentrated bone marrow specimens from any of the 6 patients in Series III, nor was *Myco. tuberculosis* cultivated from the specimens. Five of the 6 concentrated specimens were injected into guinea pigs, but no animal developed tuberculosis.

Blood study: Acid-fast organisms were not seen in the smears of the concentrated blood from any patient in this series, nor was *Myco. tuberculosis* isolated from the specimens. Animals were not inoculated with the blood specimens from patients in Series III.

Composite Data.—

Of the 24 tuberculous patients, 9 had a final diagnosis of miliary tuberculosis. One of the patients belonged to Series I which is composed of tuberculous patients without tuberculous meningitis, and the other 8 patients were tuberculous meningitis patients belonging to Series II. Acid-fast organisms were seen in the concentrated bone marrow smears of 8 of the 9 miliary tuberculosis patients, the negative smear being from a tuberculous meningitis patient who had been on antituberculosis therapy for four weeks

NONTUBERCULOUS PATIENTS

ROENTGENOGRAPHY OF LUNG	EXAMINATION FOR ACID-FAST BACILLI								REMARKS
	BONE MARROW			BLOOD		SPINAL FLUID		GASTRIC WASHINGS	
	SMEAR	CULTURE	ANIMAL INOC.	SMEAR	CULTURE	SMEAR	CULTURE	CULTURE	
Both lung fields clear	–	–	–	–	–				Brother of J. H. (Series I)
Lung fields clear	–	–	–	–	–	–	–	–	All microbiological studies were negative‡
Mottled infil. throughout both lung fields suggesting hematogenous spread	–	–	–	–	–			–	All bacteriological and mycological studies negative
Bilat. diffuse obstructive emphysema probably due to dissem. inflammatory reaction	–	–		–	–			–	*H. capsulatum* isolated from bone marrow biopsy of iliac crest
Lung fields clear	–	–	–	–	–	–	–		
No abnormality noted	–	–	–	–	–				

prior to the aspiration of the bone marrow specimen. *Myco. tuberculosis* was cultured from the bone marrow of 6 of the 8 patients with positive bone marrow smears, and the animal inoculation tests were also positive for the 6 bone marrow specimens. Both of the miliary tuberculosis patients who failed to yield *Myco. tuberculosis* by cultural methods and in whose bone marrow smears acid-fast organisms were seen had been on antituberculosis therapy. One patient had received antituberculosis drugs for six days prior to the aspiration of the specimen and the other patient had been given antituberculosis drugs for seven days. Six of the 8 miliary tuberculosis patients with positive bone marrow smears also had positive blood smears. One of those failing to give a positive blood smear had been on antituberculosis therapy for eight days prior to the aspiration of the specimen and the other had been treated for six days. *Myco. tuberculosis* was cultured from the blood of only 1 of the 9 patients with miliary tuberculosis, that being a patient without central nervous system involvement. This patient's specimen was the only blood specimen from a case of miliary tuberculosis that was introduced into an animal. The animal injected with the concentrated blood specimen developed tuberculosis.

Acid-fast bacilli were seen in the concentrated bone marrow from 8 of the

11 patients with tuberculous meningitis, and 5 of the 8 bone marrow specimens were positive for *Myco. tuberculosis,* by both cultural methods and animal inoculation. Of the 3 patients who failed to reveal acid-fast rods in the bone marrow smears, 1 had received antituberculosis therapy for four weeks. Neither of the 2 remaining patients who failed to give positive bone marrow smears had a definitive diagnosis of miliary tuberculosis and both had been on antituberculosis drugs. One patient had been treated for five days and the other for seventeen days prior to the aspiration of the bone marrow specimens. Smears of the concentrated blood were positive for acid-fast rods in 5 of the 8 patients for whom the bone marrow smears had revealed acid-fast bacilli. Two of the 3 patients who had negative blood smears had been treated with antituberculosis drugs for a week or longer prior to the aspiration of the specimen, but the third patient with a negative blood smear and a positive bone marrow smear did not have miliary tuberculosis nor had he received antituberculosis drugs. Acid-fast organisms were not isolated from the concentrated blood of any patient with tuberculous meningitis.

Of the 15 patients with nonmiliary tuberculosis, 5 had acid-fast organisms in the bone marrow smears. However, only one of these five bone marrow specimens yielded a positive culture or animal inoculation test. Of the 15 patients with nonmiliary tuberculosis, 6 had positive blood smears but *Myco. tuberculosis* was cultivated from the blood in only 1 case. Acid-fast bacilli were not seen in the bone marrow smears of this particular patient nor were they isolated from the specimen of marrow.

The 6 cases of Series III served as controls for the study since the patients of this group were nontuberculous. No acid-fast bacilli were seen in the smears of concentrated bone marrow or blood specimens from any member of this group. *Myco. tuberculosis* was not cultivated from any specimen and animals inoculated with the bone marrow specimens did not develop tuberculosis.

DISCUSSION

"From clinical and pathologic evidence it is probable that at least a few bacilli reach the blood stream in most if not all tuberculous infections during childhood," according to Lincoln.[18] Medlar[21] in writing on his concept of the pathogenesis of tuberculosis states that "an overwhelming generalized miliary tuberculosis infection and tuberculous meningitis may result from a heavy seeding of the blood stream with a probable bacteremia." According to Dubos,[12] hematogenous dissemination occurs most frequently during the progress of first infection tuberculosis and, rarely, tubercle bacilli may be cultured from the blood.

Choremis and Danelatou,[5] in discussing tuberculosis in childhood, express their particular interest in the work of other authors that discloses the relatively high frequency of positive bone marrow cultures as well as the finding of tubercle bacilli in the blood and cerebrospinal fluid in cases of primary complex without clinical manifestations. They also attempted to explain the relatively frequent occurrence of tubercle bacilli in the bone marrow of tuberculous children.

The difficulty of establishing an early diagnosis of acute miliary tuberculosis, especially in children, is well known to the clinician. Often the diagnosis is not evident until characteristic localized signs appear in the late or terminal stage of the disease, the early symptoms having been those of many generalized infections. Peterson and Canfield[24] describe a clinical type or "masquerading form" of this entity that often conceals itself behind negative chest x-rays, smears, cultures, and skin tests to be diagnosed only at postmortem.

Debre,[8] in a general discussion of miliary tuberculosis, pointed out that the tuberculin test may be negative even when the patient is not in too poor a condition. He also stated that miliary tuberculosis can be completely missed at fluoroscopy or on an imperfect x-ray film.

Many years ago, Steiner[30] pointed out the best evidence of generalized miliary tuberculosis, during life, is the demonstration by x-ray of the mottled or "snowstorm" effect in the lung fields. He emphasized, however, that this highly diagnostic feature may be absent for some time after the clinical onset in most patients and may remain absent during the entire course of the disease in which pulmonary tubercules are subsequently seen at autopsy. Not only is the radiological study of limited value in those cases in which there is failure of pulmonary localization, but the routine bacteriological examination of sputum and gastric washings is rendered useless. Even with the presence of the "snowstorm" effect of the lung radiologically, the differential diagnosis of histoplasmosis, coccidiodomycosis, tuberculosis, and similar diseases must be made. The differential diagnosis becomes more difficult in those areas where histoplasmosis is endemic. The patients considered in this study are from the geographic area where histoplasmosis infection is endemic and the clinical disease not uncommon.

The urgency of the diagnosis of acute miliary tuberculosis is emphasized by Nelson,[23] since death usually occurs within four to six weeks in untreated cases. "Whereas the mortality rate has approximated 100 per cent, recovery is now possible in the majority of instances not complicated with tuberculous meningitis if treatment is instituted sufficiently early." The association of miliary tuberculosis and tuberculous meningitis in children was demonstrated by Lincoln.[17] All physicians are aware of the seriousness of tuberculous meningitis and that the possibility of recovery depends upon the earliest possible treatment to restore the nervous system to normality before irreversible structural changes have taken place. Considering the pathogenesis of miliary tuberculosis and tuberculous meningitis, it seems probable that many if not all of these entities in children might be diagnosed by means of blood and bone marrow cultures and their recognition lead to earlier and more satisfactory treatment. The statistics recorded by many investigators would substantiate this fact.

Katz and Lifschuz[16] were highly successful in diagnosing acute hematogenous tuberculosis by means of bone marrow smear and culture. There were, however, discrepancies between the results of the bone marrow and peripheral blood studies on these patients. The authors explained that the

bacteremic phases are intermittent and of short duration so that it is uncommon to find tubercle bacilli in peripheral blood when only a single specimen has been examined.

Choremis and his co-workers have contributed greately toward the statistical evidence for the use of blood and bone marrow cultures in the diagnosis of tuberculosis. Choremis, Constantidines, and their associates,[6] were very successful in demonstrating the presence of tubercle bacilli in the blood of persons with miliary tuberculosis. Choremis and Pantazis[3] reported 324 cases of tuberculosis with 62.4 per cent positive blood cultures. They also reported culturing acid-fast bacilli from the sternal marrow of 5 of 17 patients. Choremis and Pantazis[4] a year later, reported positive bone marrow studies from 16 of 65 children most of whom had a primary complex, the others having either tuberculous pneumonia or miliary tuberculosis.

Horowitz and Goreliek[15] were successful in finding tubercle bacilli in the bone marrow of tuberculous patients. They reported that of 20 patients studied, 14 showed tubercle bacilli in the bone marrow by direct examination of the aspirated material. In 5 of the 14 cases, the diagnosis was also obtained by culture.

Choremis and Danelatou,[5] in reporting the results of a study of the laboratory diagnosis of tuberculosis in children, stated that cultures of gastric juice were more profitable in the diagnosis of the patients with a primary complex, miliary tuberculosis, and tuberculous meningitis than were the blood cultures, but not nearly as profitable as the bone marrow cultures.

The value of bone marrow aspirates is brought out in an article by Emery and Gibbs.[13] Miliary tubercles were found in the bone marrow of 13 of 44 children who were dying with generalized miliary tuberculosis. De Wan and co-workers,[9] in discussing a case of miliary tuberculosis confirmed by blood culture, emphasized that occasionally the utilization of a somewhat rare bacteriological procedure will prove a valuable adjunct to the usual methods employed. This seems to be particularly true in the diagnosis of tuberculous meningitis. The Medical Research Council[19] reported that of 92 cases of tuberculous meningitis, a diligent search for tubercle bacilli in the slide smears of the cerebrospinal fluid deposit before the start of the treatment with antituberculosis drugs, gave positive results in 42 or 46 per cent. While the direct examination of the cerebrospinal fluid smear is of great value in the diagnosis of tuberculous meningitis, many diagnoses will be delayed. Perhaps a presumptive diagnosis might be established by the examination of direct smears of concentrated blood and bone marrow, to be confirmed by cultures at a later date.

Statistical analysis of the data obtained in these experiments is not feasible because of the limited number of patients studied and the many individual differences in the subjects. The conclusions, therefore, must be of a general nature and no attempt has been made to compare the efficacy of the various laboratory methods employed in the diagnosis of tuberculosis. The prime purpose of the investigation was the study of the possibility of the use of bone marow and blood aspirates in arriving at the earliest possible diagnosis of tuberculosis in children, or of diagnosing those obscure cases where

the usual laboratory or clinical methods have failed. Perhaps a review of a few chosen cases will illustrate the value of these diagnostic procedures and encourage their use by the pediatric clinician.

CASE 1.—The opportunity to appraise bone marrow and blood aspirates as diagnostic tools arose with the timely admission to the hospital of a patient whose diagnosis was a medical enigma. This 17-month-old white male infant (J. H. of Series I) was admitted to the hospital on Jan. 5, 1952, with a history of fever for two weeks and intermittent vomiting for eight weeks. The patient had eaten poorly for almost three months. He had had a generalized convulsion on the day of admission.

The past history revealed that on Jan. 24, 1951, at the age of 6 months, the infant had been admitted to the hospital with a cough and difficulty in breathing. There was a fine macular rash on the neck and back of head and shoulders. The liver was palpable. The chest x-ray film was interpreted as a possible bronchial pneumonia. No tuberculin test reading was recorded. On Nov. 14, 1951, the patient, then 15 months of age, had been admitted to the hospital as a possible pneumonia case. He then had a history of exposure of two months to an active tuberculous patient. There was generalized lymphadenopathy, but no palpable organs. The chest x-ray film revealed a hazy infiltration of the lower right middle lung field which extended toward the hilum. The findings were compatible with acute infection of the lung. The tuberculin test (O.T. 1:1000) was negative in 48 hours as was the histoplasmin test.

The patient was critically ill at the time of this admission. The rectal temperature was 103° F. and there were fine papulonecrotic skin lesions. The patient had both hepatomegaly and splenomegaly. The clinical impression at the time of admission was most indefinite. The diseases most seriously considered in the differential diagnosis were hemosiderosis, Banti's disease, leukemia, Letterer-Siwe disease, histoplasmosis, infectious mononucleosis, lymphoma, sarcoidosis, miliary tuberculosis, and tuberculous meningitis. The tuberculin test (O.T. 1:1000) of Jan. 6, 1952, was negative at 48 hours, as was the histoplasmin test of that date. The tuberculin test (O.T. 1:1000) of January 12 was negative, as was the test using O.T. 1:100 on January 14. The x-ray film of the chest taken on the day of admission revealed a fine miliary deposit throughout both lung fields with the right hilar nodes greatly enlarged. It was suggested that the pneumonia of the previous admission was probably of tuberculous origin. Biopsy of the skin lesions revealed a nonspecific chronic inflammation. The results of the spinal fluid studies were interpreted as normal, as was the hematologic study.

The patient's condition remained critical and no definitive diagnosis had been reached after nine days of hospitalization. Miliary tuberculosis remained the most likely diagnosis from the history of exposure and the roentgenological findings in the chest. However, the continued nonreactivity to tuberculin after prolonged clinical disease was puzzling. On the ninth hospital day, January 14, blood and bone marrow aspiration was done and smears of the concentrated specimens revealed many acid-fast organisms resembling *Myco. tuberculosis*. Several of the organisms in the blood smear were intracellularly placed. These findings strengthened the diagnosis of miliary tuberculosis. Confirmation of these findings was made when, on the fourteenth day of incubation, colonies resembling those of *Myco. tuberculosis* appeared on the culture medium inoculated with concentrated blood specimen. On the seventeenth day of incubation, the medium inoculated with the bone marrow revealed growth. Animals inoculated with the concentrated

blood and bone marrow developed clinical tuberculosis. The organisms isolated from the blood and bone marrow were identified by the Communicable Disease Center Laboratory, Atlanta, Georgia, as *Myco. tuberculosis* var. *hominis*. In addition to the specimens of January 14, acid-fast organisms were seen in the blood smears of February 14, March 3, and April 1, 1952. However, the organisms were not cultivated from these specimens. Acid-fast bacilli were seen in the bone marrow smears of February 14 and March 3, but not in the specimen taken April 1, 1952. Organisms were cultivated from the bone marrow specimen of February 14.

Therapy with dihydrostreptomycin was begun January 15, the day after the acid-fast organisms were seen in the smears of bone marrow and blood. Had one waited for the isolation of *Myco. tuberculosis* from gastric washings, the diagnosis would have been delayed a month. Also, only one specimen of gastric juice out of four that were inoculated on media gave a positive culture. If a positive tuberculin test had been the confirmatory evidence, the institution of therapy would have been delayed one month and possibly two, since the negative tuberculin test did not convert until sometime between February 16 and April 7, 1952. The dates of the tuberculin tests and their interpretation are given below:

11/14/51	O.T. 1:1000	Negative
1/ 6/52	O.T. 1:1000	Negative
1/12/52	O.T. 1:1000	Negative
1/14/52	O.T. 1:100	Negative
1/29/52	O.T. 1:100	Negative
2/12/52	P.P.D. "A"	Negative
2/16/52	P.P.D. "B"	Negative
4/ 7/52	P.P.D. "B"	Positive

The patient did not respond well to the dihydrostreptomycin therapy, the hepatomegaly and splenomegaly decreasing but little after eleven weeks of treatment. Because of the unusualness of the case and the methods of isolation of the etiological agent, the attending physicians were able to procure a supply of Marsalid for therapeutic trial, the drug then being in its experimental stage. The streptomycin therapy was discontinued and Marsalid therapy started April 5, 1952. The patient responded dramatically to the new regimen of treatment and marked general improvement ensued. The patient began to eat well and to gain weight. Three weeks after the beginning of this therapy there was a tremendous decrease in the size of the liver and spleen, and after seven months of treatment the patient had recovered.

CASE 2.—J. S. of Series I, a 10-year-old Negro boy, presented an interesting problem. He was admitted to the hospital on April 24, 1952, with a history of weight loss for one month and lethargy and sleepiness in school. The past history was noncontributory except that his mother was employed by a person with far-advanced, active tuberculosis.

The admission temperature was 101° F. rectally and the principal physical findings were an enlarged liver and spleen and enlarged lymph nodes. The diseases considered in the differential diagnosis were Hodgkin's disease, histoplasmosis, sickle cell anemia, Banti's disease, leukemia, infectious mononucleosis, Boeck's sarcoid, and tuberculosis.

The x-ray study of the chest revealed extensive calcification, probably associated with an old primary infection of tuberculosis or histoplasmosis. There was no conclusive evidence of active disease of the chest. X-ray studies of the abdomen revealed calcification superimposed on the density of the spleen. The spleen and liver were greatly enlarged. Biopsy of a right axilliary lymph node was interpreted as showing no significant change. The histoplasmin test of April 24, 1952, was recorded as negative as was the tuberculin test (P.P.D. "A") applied the same day. A repeated tuberculin

test (P.P.D. "B") of May 7, 1952 was also negative. There was no evidence of granulomatous uveitis revealed by the eye examination of May 3, 1952.

Tuberculosis remained the most likely diagnosis, and blood and bone marrow aspirates were taken May 5, the eleventh hospital day. The smears of the concentrated bone marrow were negative for acid-fast organisms, and *Myco. tuberculosis* was not cultivated from the specimen. An animal injected with the concentrated bone marrow did not develop tuberculosis. Several acid-fast rods typical of *Myco. tuberculosis* were seen in the smears of the concentrated blood, some being intracellularly placed. However, the organisms were not cultivated from the blood. The finding of acid-fast rods in the blood was not conclusive evidence that the patient had an active tuberculous process, but did provide some justification for beginning antituberculosis therapy. Isonicotinic acid hydrazide treatment was started May 10, five days after acid-fast organisms were found in the blood.

A confirmatory laparotomy was performed on June 17, and the microscopic picture of the biopsied liver was that of tuberculosis. The final diagnosis was tuberculous peritonitis with hepatomegaly and splenomegaly. The usual laboratory and clinical methods contributed little toward the establishment of the diagnosis. The x-ray findings continued to be consistent with a healed primary complex and tubercle bacilli were not isolated from the gastric washings. The tuberculin test, although repeated several times, did not give a definite positive reading. The results of the tuberculin tests are recorded below:

4/24/52 P.P.D. "A" Negative
5/ 7/52 P.P.D. "B" Negative
6/ 5/52 P.P.D. "A" Negative
6/ 7/52 P.P.D. "B" 4 mm. erythema and 5 mm. induration in 48 hr.
7/19/52 O.T. 1:1000 Negative

The patient responded well to the isonicotinic acid hydrazide therapy and was discharged as cured four months after treatment was started.

The similarity between this case and one of abdominal tuberculosis reported by Choremis and Ninios[2] is noteworthy. Their patient was a 14-year-old boy with a greatly enlarged liver that was proved by biopsy to have been tuberculous. The patient gave a negative tuberculin test and, aside from the hepatomegaly, had no other signs of tuberculosis. Acid-fast bacilli were cultured from the blood, however. The tuberculin test became positive forty-five days after the beginning of streptomycin therapy and more than four months after the apparent onset of the disease, but the reaction was only weakly positive. The authors suggested that perhaps both the patient's very high sedimentation rate and his failure to react to tuberculin were related to disturbed liver function. Dittrich and Weingartner,[10] in writing on the clinical aspects and therapy of abdominal tuberculosis during childhood, emphasized that the entity frequently remains unrecognized for a considerable period of time and that the outcome of the tuberculin tests is generally weak or completely negative.

Case 3.—An 8-month-old white male (M. C. of Series II) was admitted to the hospital March 29, 1952, with the symptoms of respiratory infection. The past history was that four months prior to admission the patient developed a coryza, severe cough, and fever. The patient did not eat well and failed to gain weight. Home treatment for two months proved ineffective and the patient was taken to a physician. The patient failed to respond to a prolonged course of penicillin therapy and hospitalization was advised. There was no history of exposure to tuberculosis.

The clinical impression after the admission examination was that of tracheobronchitis, upper respiratory infection, and anemia. The liver and spleen were not palpable. The rectal

temperature was 103° F. The x-ray films of the chest taken on April 1, 1952, showed considerable infiltration in the region of the right upper lobe. There were multiple disseminated areas of miliary density throughout the remaining lung fields. The findings suggested either tuberculous pneumonia with miliary dissemination of the tuberculous process or histoplasmosis. The tuberculin test (P.P.D. "B") given March 29 was positive in 48 hours. The histoplasmin test of the same day was negative. On April 3, blood and bone marrow aspirations were done and several acid-fast rods typical of *Myco. tuberculosis* were seen in the direct smears of the concentrated specimens. Streptomycin therapy was started April 4.

The infant had no detectable meningeal involvement at the time of admission. However, because of the probable tuberculous bacillemia, the attending physicians were watchful for signs of dissemination of the organisms to the central nervous system. On April 6, the patient was found to have a stiff neck and a positive Kernig sign. There was also an elevation of temperature. The suspicion of tuberculous meningitis was strengthened by the spinal fluid findings. The spinal fluid contained 347 white cells per cubic millimeter, of which 74 per cent were polymorphonuclear leukocytes and 26 per cent lymphocytes. The total protein was 116 mg. per cent, the sugar 25 mg. per cent, and the chlorides 105 mEq. per liter. No acid-fast organisms were found in the spinal fluid, although a diligent search was made. The electroencephalogram of April 10 was interpreted as being compatible with a moderately severe encephalopathy. The regimen of treatment was changed with the development of meningitis, isonicotinic acid hydrazide being substituted for the streptomycin.

Although bacteriological studies were done on four specimens of gastric washings, acid-fast organisms were never isolated from the gastric juice. The etiological agent of the pneumonic process, therefore, could not be identified by this diagnostic procedure. The final identification of the etiological agent of the meningitis was not established until twenty days after the onset of this complication when *Myco. tuberculosis* was isolated from the spinal fluid. *Myco. tuberculosis* was cultivated from the bone marrow specimen and an animal inoculated with the marrow specimen developed tuberculosis. The growth of the organisms on the medium inoculated with the bone marrow specimen was more rapid than on the medium inoculated with the spinal fluid, colonies appearing in fifteen days in the former case as compared to twenty days in the latter.

The patient's improvement was rapid and the recovery from the meningitis was without sequelae. The early recognition of the meningeal complication and the presumptive identification of its etiological agent by means of bone marrow and blood aspirates was believed highly contributory to the successful treatment of the patient.

In a number of cases, acid-fast rods typical of *Myco tuberculosis* seen in the direct smears of concentrated blood and bone marrow were not cultivated from the clinical specimen. The final identification of acid-fast rods as *Myco. tuberculosis* depends upon the isolation and study of the organism, and the identification by microscopic means alone is only presumptive. However, specimens from enclosed spaces such as pleural, spinal, peritoneal, and joint fluids are not nearly as subject to false positive findings as stomach washings, sputum and urine. According to Smith,[29] the presence of nonpathogenic acid-fast bacilli in specimens from enclosed spaces is so rare that for practical purposes they may be almost ignored. "Provided the equipment and technic

are above suspicion, the microscopic demonstration of a few typical acid-fast bacilli will make the diagnosis of tuberculosis highly probable."

There are several proposed ideas to explain the failure to isolate on artificial culture media the acid-fast organisms seen in clinical specimens. Of course, the use of tuberculostatic drugs will explain many of the failures of isolation technique. As has been pointed out by Dubos,[11] it is much more difficult to initiate growth on artificial media seeded with minute inocula containing only a few living organisms than it is to isolate organisms from large inocula of either a culture or pathologic material. The sparsity of organisms in blood and bone marrow specimens might explain some of the difficulties encountered in this investigation. Another factor often overlooked is the rise in temperature of the specimen that is being centrifuged at high speed for long periods in an instrument with a horizontal head. This point was emphasized in an article published by the Public Health Laboratory Service.[25]

Schneider[28] warned against the use of too high concentration of malachite green in the media inoculated with bone marrow and blood specimens. Another explanation for the inability to cultivate the acid-fast organisms seen in the clinical specimens is that the spermine content of the blood and bone marrow might be sufficiently high to act as a tuberculostatic agent. Many papers have been published on the bactericidal effect of the concentrating or homogenizing agents used in the isolation of pathogenic acid-fast bacilli. Even the commonly used substance sodium hydroxide is not innocuous. Medlar and co-workers,[20] in quoting a passage from an article by Canetti, offer a plausible explanation for the failure to always culture from clinical material the organisms seen on direct smear:

> "There exist in numerous tuberculous lesions of man some bacilli which when inoculated on artificial media do not produce colonies at the moment. It is possible that a greater number of these bacilli are dead and as to the others which are still alive their ability to reproduce is greatly lessened. Concerning the acid-fast bacilli which we see in the tuberculous lesion, there are those that are dead and subject to disintegration; others that are living but are unable to reproduce, and some at the time are living and are plainly able to reproduce."

SUMMARY AND CONCLUSIONS

The 30 patients of this investigation are categorized into three groups or series. Series I is composed of 13 children who had tuberculosis that was uncomplicated by meningitis. Smears of the concentrated bone marrow were positive for acid-fast bacilli in 5 of the 13 cases, and 2 of the 5 specimens were positive for *Myco. tuberculosis* by both cultural methods and animal inoculation. Smears of the concentrated blood were positive for acid-fast rods in 7 of the 13 cases and *Myco. tuberculosis* was isolated from 2 of the 7 cases with positive blood smears.

Series II is composed of 11 children who had a final diagnosis of tuberculous meningitis. Smears of the concentrated bone marrow specimens were positive for acid-fast rods in 8 of the 11 patients of this group, and 5 of the 8 were positive for *Myco. tuberculosis* by both cultural methods and animal inoculation. Smears of the concentrated blood were positive

for acid-fast rods in 5 of the 8 patients for whom the bone marrow smears were positive, but *Myco. tuberculosis* was not isolated from the blood specimens.

The 6 cases of Series III served as controls for this study since the patients of the group were nontuberculous. Acid-fast bacilli were not seen in the clinical specimens nor were they isolated by either culture or animal inoculation.

The results indicate that bone marrow and blood aspiration techniques probably have their greatest application and usefulness in the diagnosis of miliary tuberculosis. Of the 24 tuberculous patients in this study, 9 had a final diagnosis of miliary tuberculosis. Acid-fast bacilli were seen in the concentrated bone marrow smears of 8 of these 9 patients, the negative smear being from a tuberculous meningitis patient who had been on antituberculosis therapy for four weeks prior to the aspiration of the specimens. *Myco. tuberculosis* was cultured from the bone marrow of 6 of the 8 patients with positive smears, and the animal inoculation tests were also positive for the 6 bone marrow specimens. The patients who failed to yield positive cultures had been on antituberculosis therapy for at least a week. Six of 8 miliary tuberculosis patients with positive bone marrow smears also had positive blood smears, the 2 failing to yield positive smears had been treated for a week. *Myco. tuberculosis* was cultured from the blood of only 1 patient with miliary tuberculosis.

To illustrate the usefulness of bone marrow and blood aspirates in the diagnosis of tuberculosis in children, the case histories of 3 patients were reviewed. The final diagnoses of the cases selected were miliary tuberculosis, tuberculous peritonitis, and tuberculous meningitis.

An attempt was made to explain the failure to isolate on artificial culture media or by animal inoculation the acid-fast organisms seen in clinical specimens, thereby rendering a definitive bacteriological diagnosis of tuberculosis impossible.

Although the number of clinical cases is limited, the results of this investigation indicate that bone marrow and blood aspirates are useful in establishing the diagnosis of tuberculosis in children. These methods are not offered as substitutes for the usual laboratory procedures, but they provide additional sources of information if the study of the routine specimens proves unrewarding. The methods are especially valuable in the entities tuberculous meningitis and miliary tuberculosis where the patient's life is dependent upon the early recognition and treatment of the disease.

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SURGICAL TREATMENT OF SOME PULMONARY CONDITIONS IN CHILDHOOD

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RESPIRATORY infections in children are so commonplace, and standard therapy so effective, that specific anatomic or pathologic causes for such infection are rarely sought. However, such a search in children with repeated severe infections may be far from unrewarding. Within a recent twelve months' period, four different intrathoracic lesions in children have been encountered at Misericordia Hospital. Three of these have been the bases for repeated pulmonary infections. All have been definitively treated by operation. Although the standard roentgenogram of the chest disclosed two of these lesions, it has taken a measure of clinical suspicion and nonroutine roentgenologic study to demonstrate the other two. These studies have been simple to perform, but have been most efficient in demonstrating the lesions.

It is believed that a report of these cases may stimulate a more active search for specific etiology in recurrent respiratory infections in children.

Case 1.—B. N. weighed 4,100 grams at birth on Oct. 30, 1955. He spent an unremarkable immediate postnatal course, and at the time of his discharge examination on the fifth day the examining pediatrician found no pulmonary disease. At the time of the baby's six months' visit the mother reported a mild, dry cough for the preceding three or four weeks, and a failure to gain weight as rapidly as he had prior to that time. There was no dyspnea or cyanosis, and the child appeared generally healthy, although small for his age. The point of maximal cardiac impulse was found to lie to the right of the sternum, and there was a hyperresonance over the entire left thorax. A chest roentgenogram taken two days later showed an enormous cystic lesion occupying the left thorax (Fig. 1). Mediastinal structures were displaced beyond the midline to the right, compressing the right lung to about one-third of its normal expected volume. The margins of the cyst were visible on the roentgenogram as linear streaks.

On May 9, 1956, thoracotomy was performed under endotracheal anesthesia. The major operative finding was a huge cystic lesion of the left lower lobe which compressed the left upper lobe so that it was totally atelectatic. The mediastinum was displaced and the left diaphragm depressed. Left lower lobectomy was performed. At the conclusion of the lobectomy, the upper lobe could be expanded under pressure.

Recovery was rapid and uncomplicated. By the first postoperative day, the mediastinal structures had returned to the midline. The left upper lobe remained well expanded, filling more than half of the left thorax. The previously compressed lung was now fully expanded.

Pathologic examination confirmed the clinical impression of congenital

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pulmonary cyst. The specimen was described as an irregular pyramidal, cystic mass, measuring 10 by 5 by 6 cm. On one surface there was a recognizable bronchus and recognizable lung tissue. No bronchial connection could be demonstrated. Microscopically the cyst was found to be lined by columnar epithelium, beneath which there was a layer of smooth muscle, indicating the bronchial origin of the cyst.

The solitary congenital pulmonary cyst results from a cystic dilatation of an underdeveloped bronchopulmonary segment by an accumulation of air or of fluid secreted by the lining epithelial cells.[1] These cysts may become evident shortly after birth if they occupy a major portion of one lung at that time. If the cyst is so small that pulmonary physiology is undisturbed, or if it

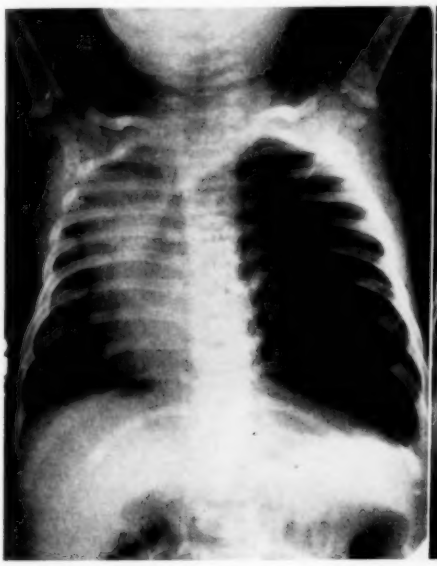

Fig. 1.

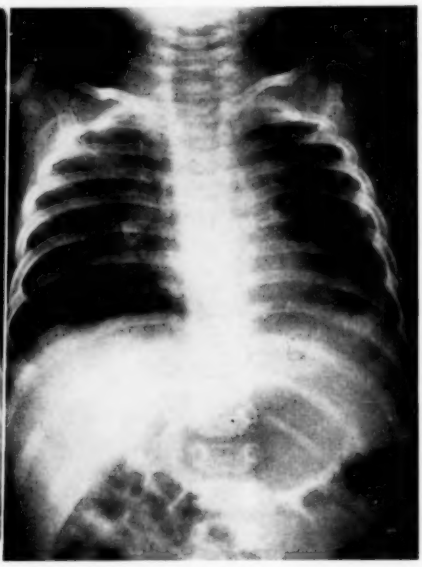

Fig. 2.

Fig. 1.—Case 1. This preoperative roentgenogram illustrates the large size of the pulmonary cyst. The left diaphragm is depressed and the mediastinum is displaced well into the right hemithorax.

Fig. 2.—Case 1. The postoperative roentgenogram shows a normally placed mediastinum and an adequately aerated left hemithorax.

The baby was discharged twelve days after operation to the care of his pediatrician. Three months postoperatively, he was well, gaining weight, and entirely asymptomatic. Chest roentgenogram at this time showed normal position of all mediastinal structures. The left upper lobe was well expanded and filled the major part of the left thorax (Fig. 2).

enlarges slowly, its presence may not be manifest for years. With progressive distention of the cyst, there will be recurrent attacks of cyanosis, dyspnea, and cough. In the infant, this cyanosis and dyspnea will be noted following a period of crying or struggling during which additional air may enter the cyst and cannot be released

because of the valvular action at the bronchial communication. The bronchial communication is also the source of the inevitable infection arising in such cysts. The normally developed lung, rendered increasingly atelectatic by the enlarging cyst, is likewise a prime site for recurrent infections.

This large lesion in our patient was causing no particular symptoms, but the marked displacement of the intrathoracic structures and the presumed rapid enlargement of the cyst in a period of six months made the future development of serious symptoms inevitable. Surgical excision should result in a permanent cure. Delaying operation until the appearance of complications such as infection, hemorrhage, or pneumothorax would be most unwise as surgical experience has demonstrated a high mortality in those in whom complications have supervened.[2, 3]

CASE 2.—M. M. a 2-year-old girl, was admitted to Misericordia Hospital on Dec. 28, 1956, with a diagnosis of lobar pneumonia. She had been hospitalized three months earlier with the same diagnosis, and presented a long history of frequent, less severe pulmonary infections. Her presenting complaints at this admission were fever, cough, dyspnea, lethargy, and anorexia. The rectal temperature was 104.6° F., and the child appeared pale and ill. The examining physician reported decreased excursion of the left hemithorax and diminished breath sounds over the left base. The initial chest roentgenogram disclosed left lower lobe atelectasis and pneumonia and a marked emphysema of the remainder of the left lung (Fig. 3). The patient responded well to antibiotic therapy, but continued to cough frequently. Her voice was noted to have a peculiar hoarseness, and she vomited one or more times daily. However, the atelectasis and emphysema persisted, and bronchoscopy was advised to search for a possible radiolucent foreign body. No intrinsic lesion or foreign body was visualized by the bronchoscopist.* The impression was compression stenosis of the left lower lobe bronchus. Fluoroscopic examination again disclosed increased aeration of the left lung and its failure to empty during normal respiration. There was a mass lesion demonstrated in the left side of the mediastinun by the esophagram. This lesion appeared to be above the left main bronchus, and anterior and to the left of the esophagus. The soft tissue mass produced a pressure effect on the midportion of the esophagus, displacing it toward the right and posteriorly (Fig. 4). Bronchogram two days later showed prompt passage of the Lipiodol into the right main bronchus and its branches, and a delayed passage of it into the left lung. None of the smaller bronchi could be outlined on the left side, and a shallow indentation of the superior border of the left main bronchus was seen.

On Jan. 22, 1957, under endotracheal anesthesia, thoracotomy was performed through the left fourth interspace. The left lung collapsed slowly and with difficulty. A soft, cystic spherical lesion was palpable posterior to the lung root, and inferior to the aortic arch. Continued dissection revealed the cystic lesion to have most intimate points of attachment to the esophagus posteriorly, and to the trachea anteriorly, with no connection with the lumen of either. Excision was completed, and the mediastinal pleura loosely closed over the apparent defect between trachea and esophagus.

Pathologic examination revealed the thin-walled, cystic mass to measure 3.5 by 3 by 3 cm., and to be filled with an opaque, white mucoid fluid. The lining was faintly trabeculated.

*Bronchoscopy was performed by Dr. John J. O'Keefe.

Microscopically, the lining was typical respiratory epithelium with small numbers of mucous glands, and the diagnosis of bronchogenic cyst was confirmed.

The postoperative course was benign. Nine days after thoracotomy, repeat eosphagram demonstrated no deformity or displacement. The lung fields at this time showed no evidence of atelectasis, emphysema, or any other abnormality. The patient was discharged on the tenth postoperative day and has been in good health since that time.

Bronchogenic cysts are congenital malformations arising from the re-

Fig. 3.

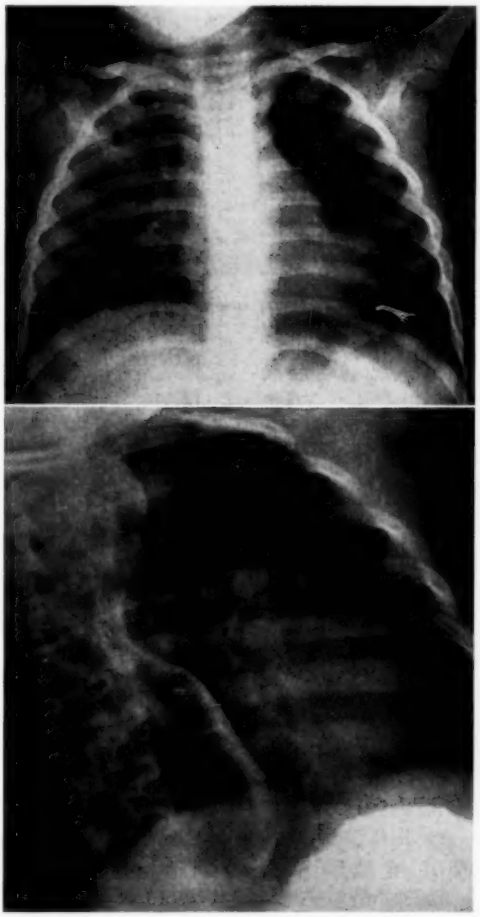

Fig. 4.

Fig. 3.—Case 2. The excessive aeration of the left lung may be seen in the posteroanterior roentgenogram of the chest. There is no apparent abnormality of the mediastinal structure.

Fig. 4.—Case 2. The barium-coated esophagus is displaced in its mid-portion by a mass. There is slight narrowing of the esophagus also at this point. This mass was proved to be a bronchogenic cyst.

spiratory tract because of an abnormal budding of the tracheobronchial tree.[4] The mediastinal cysts generally have no communication with the bronchial lumen, and increase in size because of the accumulating secretions within the cavity. These cysts lie in proximity to the lower part of the trachea or main bronchi, generally in such a confined space that symptoms may be apparent in the infant long before the cysts are large enough to be easily demonstrable on routine roentgenograms. The bronchogenic cyst never approaches the size of the pulmonary cyst, but causes difficulties either because of pressure on vital structures or because of the development of such complications as infection, rupture of the cyst, bronchial fistula formation or empyema. In small children, in addition to the usual findings of cough, dyspnea, and repeated pulmonary infections secondary to compression of trachea or bronchi, dysphagia and vomiting are also common complaints since the cyst so frequently distorts the esophagus. The accepted treatment of bronchogenic cysts is surgical excision.

This second patient is an excellent example of a child whose repeated infections had a specific etiology. Compression of the left main bronchus permitted recurrent infections in that lung. Despite this, the standard chest roentgenogram gave no clue to the existence of the mediastinal lesion. Because the respiratory infections were severe and recurrent, a definite attempt was made to find a lesion. Bronchoscopy was helpful in a negative way. The bronchograms were helpful but not diagnostic. The esophagram, however, clearly outlined the cyst. Bronchogenic cysts may remain asymptomatic, yet their strategic location in a relatively confined space between the esophagus and the tracheal bifurcation makes them a potential source of real trouble.

CASE 3.—B. C., a 6-year-old girl, was readmitted to Misericordia Hospital on Feb. 28, 1957, because of weekly bouts of fever for approximately four months. An associated symptom was cough, occasionally productive of rusty sputum. On admission, she was afebrile and no lesion was detected in the lung on physical examination. Chest roentgenogram demonstrated an increased degree of aeration in the right upper lobe (Fig. 5). This was interpreted as emphysema. Esophagram was normal. Bronchoscopy ruled out foreign body or bronchial stenosis.

At operation, March 25, 1957, free bubbles of air could be seen beneath the entire extent of the visceral pleura of the right upper lobe. No specific cause could be found for this emphysema either in the lobe or in the mediastinum, and the right upper and middle lobes were removed. Pathologic study of the diseased upper lobe revealed extensive emphysema, ruptured alveoli, and a moderate inflammatory reaction about the bronchi. Her postoperative course was smooth, and she was discharged ten days after operation. She has remained well since that time.

Although a suitable single explanation for the development of congenital lobar emphysema is lacking, it produces the usual complications of inadequate pulmonary ventilation. These complications are seen most commonly in infants, and less frequently in older children. Generally no cause other than the faulty development of the affected lung can be demonstrated. Since the congenitally emphysematous

lobe remains uniformly pink and overdistended after excision, it has been suggested that some intrinsic abnormality of elastic tissue may be a factor in its development.[5]

Clinically the condition may be suspected in the infant who exhibits progressively severe dyspnea with findings of segmental emphysema, compensatory atelectasis in the compressed adjacent lung, and mediastinal shift.

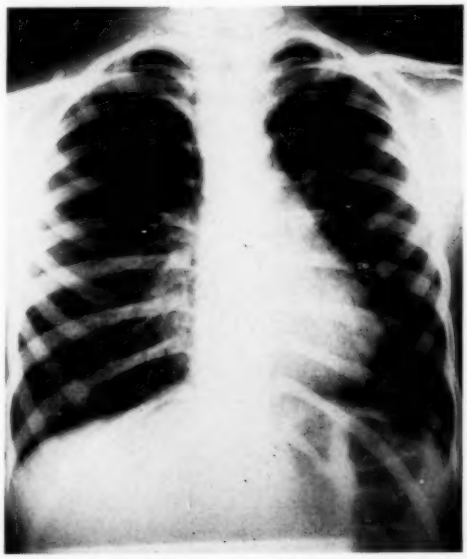

Fig. 5.—Case 3. The only abnormality to be seen is excessive aeration of the lung in the region of the right upper lobe. The mediastinum seems to be in its normal position. At operation, the right upper lobe was found to be the site of extensive emphysema.

The roentgen findings may simulate pneumothorax or atelectasis of the opposite side. Congenital pulmonary emphysema may present as an acute respiratory emergency shortly after birth. The most dramatic results have been obtained in lobectomies performed in newborn infants when this entity had been causing a hypoxia incompatible with continued life.[6]

The area of radiolucency may be noted to be in the distribution of a single lobe, but frequently the lobe is so overdistended that it is difficult to recognize it as such. Careful examination of the roentgenograms reveals lung markings throughout the entire area, distinguishing it from pneumothorax or cystic disease.

Fischer, Potts, and Holinger[7] indicate their belief that the idiopathic congenital lobar emphysema is the same entity as that produced by some bronchial abnormality or intrathoracic vascular lesion. They demonstrated deficiency of the cartilagenous rings of the bronchus in two cases, a persistent ductus arteriosus overlying the left main bronchus in two cases, and no demonstrable bronchial or any other intrathoracic lesion in three cases. This opinion is at variance with that of several other authors who conceive of this emphysema as an intrinsically faulty development of this part of the

lung rather than as a consequence of bronchial obstruction.[8, 9] Findings at thoracotomy and subsequent pathological examination of the removed specimen in our case would support the second hypothesis.

A report by Gilbert and Myers[10] lends additional support to the plea for early diagnosis before irreversible changes require the sacrifice of more pulmonary tissue. These writers suggest that the primary disability in their case was atelectasis which became less amenable to relief as the compensatory emphysema increased.

Symptoms are relieved by the removal of the affected lobe with the release of the compression upon the normal lobes. No instance of recurrence of symptoms or development of the emphysema in other lobes has been reported.

In this patient, although no specific anatomic nor physiologic lesion could be found to explain the etiology of the emphysema, the extensive character of the pulmonary changes in the right upper lobe were obviously irreversible, and would, if left in situ, be responsible for repeated pulmonary infections. Extirpation seemed warranted, and the result to date has been good.

CASE 4.—D. F., a female infant, was admitted to the Misericordia Hospital on April 4, 1957, at the age of 6 weeks, with a two-day history of fever and noisy respirations. She had previously seemed in good health. On admission, her breathing was labored and râles and rhonchi could be heard throughout both lung fields. There was no cyanosis. Chest roentgenogram was negative. Her fever responded to antibiotics, but her breathing remained noisy as though there were considerable tracheal mucus. Further roentgenological studies included an esophagram which disclosed a constant narrow extrinsic defect in the esophagus posteriorly at the level of the aortic arch, and a defect in the anterior tracheal wall at the same level (Fig. 6).

A diagnosis of double aortic arch or other "vascular ring" was made. On May 13, 1957, exploration was done under endotracheal anesthesia. A double aortic arch was found, and the most peripheral segment of the anterior and smaller arch was severed, freeing the esophagus and trachea. Postoperatively, the infant's breathing was much easier and quiet, and there has been no recurrence of her respiratory stridor. She is developing normally and remains asymptomatic.

Double aortic arch is a congenital anomaly in which, because of persistence of both right and left embryonic arches, the ascending aorta divides so that one branch passes anterior to the trachea to the left, and one posterior to the esophagus to the right, subsequently joining to form the descending aorta.[11]

Although the anomaly of double aortic arch may exist without causing symptoms in certain instances, generally both trachea and esophagus are compressed so that tracheal obstruction and attendant pulmonary infection often cause death within the first year of life. Ferguson and Flake[12] believe that by far the commonest extralaryngeal causes of stridor are to be found in patients who have a compression of the trachea by an abnormal aortic arch, and that the earliest and most severe symptoms of tracheal obstruction are seen in infants with this anomaly. The first evidences of tracheal compression and pulmonary infection may suggest a routine tracheobronchitis; however, in these patients, stridor persists after infection

has been controlled, and respiratory distress is aggravated by feeding. The infant, even one so young as the case presented here, lies more comfortably in a semiprone position with marked hyperextension of the head which improves the airway, and the child becomes obviously distressed when placed supine or when the head is flexed.

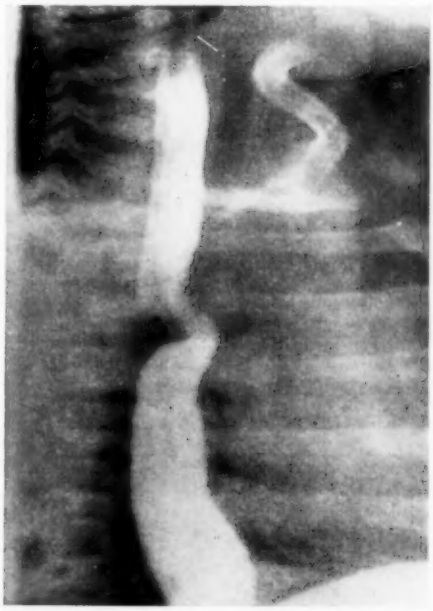

Fig. 6.—Case 4. The esophagus is indented posteriorly. It is displaced and narrowed at the same level that the tracheal air column is narrowed. The lesion is a double aortic arch.

Plain roentgenograms of the chest may show only an associated pneumonitis. Roentgenograms with contrast media will demonstrate indentation of the posterior wall of the esophagus and compression of the trachea anteriorly and laterally in the lower third.

Surgery is particularly gratifying in these patients because simple division of the smaller arch provides the necessary room for trachea and esophagus. The remaining vascular system is physiologically adequate, and the trachea is allowed to grow normally since extrinsic pressure has been removed. Unless this anomaly is sought and corrected when minimal compression causes symptoms, the encroachment upon the trachea may progress to a degree resulting in fatal complications during infancy.

Each of these four cases might conceivably have been treated by some temporary measure to relieve the presenting symptoms occasioned by the complications rather than the basic disease. However, it is certain that each patient would have been in need of definitive surgery at some later date and as a poorer risk. The awareness of a surgically remediable lesion in an infant with progressive respiratory distress, or repeated severe pulmonary

infections marks the first step of the cure. The conventional chest roentgenogram may fail to identify the true nature of the disease in its early stages. However, supplementary studies with fluoroscopy and contrast visualization of the esophagus and tracheobronchial tree will yield a marked increase in early diagnoses. Infants do not tolerate hypoxia without early brain damage, making it important to correct the disorder as soon as possible. Moreover, with increase of emphysematous lung areas, normal lung is jeopardized by prolonged atelectasis.

It is not difficult to believe that many instances of surgically correctable malformations have been responsible for deaths listed as pneumonia, bronchial asthma, tracheobronchitis, or unidentified respiratory obstructions. A more active search for such lesions as the underlying causes of repeated pulmonary infections in infants should be a rewarding endeavor.

SUMMARY

Four cases of surgically correctable intrathoracic lesions in young children are presented. Three of these had caused repeated pulmonary infections and respiratory distress. The fourth, although asymptomatic at discovery, would soon have become evident because of rapid encroachment upon remaining normal pulmonary tissue. Conventional chest roentgenogram and, in two instances, supplementary information from contrast visualization of trachea and esophagus confirmed the diagnosis. Surgical correction of the basic lesion resulted in cure in all cases. It is suggested that these relatively simple diagnostic studies be made in children with repeated unexplained pulmonary infections.

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A TERMINOLOGY AND DIFFERENTIAL DIAGNOSIS FOR BRIEF SEIZURES IN INFANTS AND CHILDREN; AND THE DEFINITION OF PETIT MAL

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PROPER management of patients with convulsive attacks requires that the physician be aware of the nature of various clinical seizure types. There is a confusion in the terminology applied to brief seizures which are not full generalized major seizures. This is a handicap to the physician who cares for infants and children with brief seizures. Traditionally the terms "minor seizure" and "petit mal" have been used to designate any brief convulsive attack which lacks the spectacular features of a grand mal attack. In this sense these terms are being used in an effort to characterize the severity of seizures in a roughly quantitative way. These uses of the terms "petit mal" and "minor seizure" imply what is not true, namely that all brief seizures are of similar significance and that the treatment and prognosis are identical in all brief attacks. This confused terminology makes certain statements about treatment and prognosis irreconcilable. The same name is being used for different types of attacks and different names are being used for the same type of attack.

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Because of lack of basic knowledge, no classification system of seizures that can be presently constructed is ideal or completely consistent. It would seem, in fact, that even the attempt to classify seizures into "major" and "minor" categories has no truly logical basis and separates attack patterns arbitrarily and artificially. There can be no argument that a typical grand mal attack is a "major" seizure or a "major motor" seizure. However, a focal motor seizure which may be extremely short, involve only a very limited part of the body, produce no injury, and leave the sufferer fully conscious may be called a variety of "major motor" seizure; whereas a massive myoclonic seizure which may throw its unconscious victim to the floor with injurious force may be called a "minor motor" seizure.[1] Buchanan's[2] organization of the various forms of convulsive attacks in the order of their extent has some logic to it, as does his separation into "major" and "minor" categories on a basis of whether or not the victim falls down in the attack.

The clinician will do best to characterize attacks and their victims as fully as he can, and not be concerned with whether the attack is "major" or "minor." If the attack and its

victim are described fully, treatment and prognosis will be facilitated.

Classification on clinical grounds is more reliable and useful than classification based on electroencephalography, etiology (often only presumed), or on site of origin within the nervous system (also often only presumed). For example, spike and wave patterns are seen in electroencephalograms of conditions that are remarkably dissimilar clinically.

They may be so infrequent and brief that neither the patient nor others are aware of them; or they may occur hundreds of times an hour. The attacks last 5 to 30 seconds, consciousness is lost, and slight pallor may occur. The eyes stare ahead and may roll up, or there may be a 3-per-second beat of the eyelids and head and more rarely the arms. The patient does not fall down unless he is in some peculiar position at the time of the attack.

TABLE I. TYPES OF BRIEF SEIZURES

1.	2.	3.	4.	5.	6.
Petit mal	Abortive major	Psychomotor attacks	Simple myoclonic	Akinetic	Massive myoclonic
	Incomplete major	Temporal lobe seizures		Atonic	Infantile myoclonic
				Static	Infantile spasms
				Drop	
				Head drop	
				Salaam	
				Inhibitory	

Table I gives the names of what are usually brief attacks. Where more than one name appears in the same column, it is because the author feels that the various terms are essentially synonymous in current usage.

1. *Petit Mal.*—A disease which is clinically distinct from all other diseases should be designated by a name which is then not used for any other disorder. There is one type of brief seizure disorder that is unique in the virtually unvarying characteristics of the attack, of the electroencephalogram, and of the subjects of the attacks. For this condition the name "petit mal" ought to be reserved. Livingston[1] uses the term in this sense, but few others who write about convulsions do. "It is epilepsy in its purest form."[2]

Petit mal attacks are basically staring spells. The patient stops what he is doing, stares, and then resumes his activity with little loss of continuity. There is no aura, and there are no postictal phenomena; the patient is quite clear when the attack ends. The attacks may occur in bursts where one attack follows immediately upon another and the patient is unconscious for periods of minutes to days. Attacks tend to occur just after sleep. The ratio of attacks in girls as compared to boys is about 3:1. Petit mal does not begin under the age of 3 years[1] nor after full maturity is reached. Mentality is normal, and remains that way. Organic central nervous system disease is not found by any present method of investigation; brief attacks coming on after serious brain damage are not true petit mal. The attacks can be precipitated by hyperventilation. The methadione drugs seem to have a specific effect against petit mal (though not in 100 per cent of cases) and are ineffective in other kinds of attacks. The drugs effective against grand mal

attacks (barbiturates, hydantoins, etc.) may reduce the frequency of petit mal, but only temporarily, and often aggravate the disorder. The electroencephalogram in petit mal shows in all leads a monotonously regular 3 per second spike and wave pattern. This pattern, if it does not occur spontaneously, may be produced by hyperventilation.

The diagnosis of true petit mal is not likely to be correct if the clinical picture does not correspond almost exactly to this description. Thus, the presence alone or together of mental retardation, organic brain disease, falling in attacks, onset under the age of 3 years, aura, postictal phenomena, conspicuous or widespread muscular rigidity or movement, or spike and wave patterns in the electroencephalogram at frequencies other than 3 per second invalidate the diagnosis.

2. *Abortive or Incomplete Major Seizures.*—Some patients who are started on treatment for grand mal attacks have disappearance of the full attack, but then have "absences," or brief attacks of stiffening without falling, or sudden rolling up of the eyes, or clonic contractions of various muscle groups. It is sometimes stated that therapy for the grand mal has uncovered or precipitated "petit mal." Often it is only necessary to increase the dosage of the drugs being employed to cause disappearance of the brief attacks. In this situation the brief attacks can be truly called abortive or incomplete major seizures.

It seems not to be generally recognized that all the features of a grand mal attack may not appear in every attack. The various features may occur singly or in all possible combinations. If a child is known to suffer from grand mal, brief attacks are likely to be incomplete or abortive major attacks rather than some additional type of convulsive disorder. Diagnosis is less certain if the abortive attacks occur prior to the first full grand mal seizure. This is particularly true if only the aura is experienced.

3. *Psychomotor Seizures.*—Long psychomotor attacks in children may be difficult to distinguish from behavior disorders, but will not be confused with petit mal. With shorter psychomotor attacks, such confusion is likely. Brief attacks in which there is lip smacking, fumbling of the hands, vocalization, confused wandering about, with a slow return to rationalness should suggest that the attack is psychomotor in nature and is not true petit mal.

4. *Simple or Single Myoclonic Seizures.*—In these attacks there are contractions of isolated flexor muscles. Consciousness is not lost. They occur most often just after sleep and resemble the jerks many people experience while falling asleep. They often occur in children who also have grand mal attacks. When simple myoclonic jerks originate at a cerebral level (the electroencephalogram may show a single spike and dome at the time of an attack), they probably are abortive major attacks. When they arise at a spinal cord level, as they may,[4] they probably deserve a special name, and the above name is as good as any.

5. *Akinetic Attacks.*—In these attacks there is a sudden loss of postural tone and the patient falls forward to the floor precipitously. If the patient is sitting at the time of an attack, his

head and trunk slump forward. These attacks often begin under 3 years of age. Consciousness is lost. The age and mental condition of affected children is frequently such that no information can be obtained about an aura, although, if the child is capable of walking, he may run toward his mother just before an attack. This is evidence that the child experiences some warning of an impending attack. The patient usually is able to rise within seconds after falling. Serious mental deficiency and other evidences of organic brain damage are usually present. These attacks may occur many times an hour, and prevention of repeated injury is difficult.

6. *Infantile Myoclonic Seizures.*—Clinically, these look like an exaggerated startle response of infancy and, indeed, may be misdiagnosed as this in early life. There is a sudden flexion and adduction of the arms, flexion of the trunk, and flexion of the thighs. The face is blank and a piercing cry may be heard. These attacks tend to occur many dozens of times a day. Infants with these attacks are severely retarded mentally, almost without exception. Whether this retardation is present before the attacks begin or whether actual mental deterioration occurs is an important question.[5, 6]

The electroencephalograms of patients with attacks as described under (5) and (6) above show a variety of abnormalities. Spike and wave patterns, if they occur, are at frequencies other than 3 per second.

There are three distressing features of the brief seizures other than petit mal described under (5) and (6) above: (1) Infants and children with these attacks usually have mental retardation, often severe, and this proves ultimately to be more important than the seizures. The seizures

TABLE II

CHARACTERISTIC	PETIT MAL	OTHER BRIEF ATTACKS
1. Duration	5-30 seconds	Same or longer
2. Electroencephalogram	3 per second spike and wave	Variable. Spikes and waves atypical if present
3. Consciousness	Lost	Usually lost, but variable
4. Skin color	Pallor	Pallor
5. Eyes	Roll up or stare	Same; and may close
6. Movement	Beat of head and eyelids at 3 per second	Variable; see text
7. Postural tone	Not lost	Variable, but usually lost except in psychomotors
8. Injury	Does not occur	Usually occurs, except in psychomotors
9. Aura	None	Variable, but may be present
10. Postictal phenomena	None	Frequent
11. Relationship to sleep	Most frequent just after awakening	Not consistent
12. Sex ratio (girls:boys)	3:1	1:1
13. Relationship to age	Rarely under 3 years	Often under 3 years, except psychomotors
14. Mentality	Normal	Often defective
15. Organic central nervous system disorders	Never found	Often found
16. Effect of hyperventilation	Precipitates attack	Indifferent
17. Effect of methadiones	Specific	Little or no effect
18. Effect of drugs used for grand mal	Temporarily benefit and then aggravate	Some useful effect in large doses

may diminish or disappear as time goes by. (2) Serious injury occurs repeatedly if and when the child is able to stand. (3) No satisfactory treatment for these seizures is available. The methadiones are ineffective. The attacks are lessened only by drug dosages that produce intolerable stupor and ataxia.

Table II summarizes the important differences between true petit mal and other brief seizures.

SUMMARY

The terminology of convulsive disorders probably will remain confused until more basic information is available. The confusion could be lessened if the term "petit mal" were restricted to what is a clinically distinct seizure disorder. Similarly, the confusion would be less if no attempt were made to force seizures arbitrarily into a "major" and "minor" classification. The clinician's efforts should be directed toward a full characterization of the attack and its victim. The knowledge thus gained will help the physician predict the future for his patient and employ the most effective of the available therapies.

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PROLAPSING TRIGONAL MUCOSA IN INFANT

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PROLAPSING trigonal mucosa is apparently a rather unusual phenomenon. A careful search of the available literature for this subject yielded only reports in which redundant mucosa was found to be strictly within the bladder cavity. In 1933, Harris[3] described a case wherein mucosal redundancy formed a cupping at the anterior trigone. A similar case was reported by Beer[2] in an 8-year-old boy. In 1937, Campbell[9] cited 6 instances of redundant trigonal mucosa found at autopsy. Four occurred in boys. In a case which we recently encountered, folds of trigonal mucosa were found not only to be redundant but also to prolapse through the urethra into the vagina upon straining. The rarity of such an occurrence served as a stimulus for this publication.

CASE REPORT

E. R. (No. 8715), an 11-month-old girl, was brought by her mother to Blanco Hospital, Cebu City, Philippines, on Nov. 11, 1956, because of a mass that protruded from the vagina whenever the child strained. Our first examination failed to reveal the presence of the mass but continued observation showed the mother's description to be accurate.

The child was claimed to be in apparently good health until 5 months prior to her admission to the hospital when she was observed to strain during urination. This straining became progressively so marked that at times urination would come simultaneously with bowel movement. The child had repeated episodes of low-grade fever and pyuria. In August, 1956, one month after the onset of the illness, the mother noticed for the first time a mass projecting from the vagina. The mass increased in size upon continued straining. In another hospital where the child was first admitted, a diagnosis of prolapsing ureterocele or urethrocele was entertained and operation was advised but was promptly refused.

The infant's birth was spontaneous at 9 months' gestation. She was breast-fed and had accordingly been developing normally until the onset of the present illness. She was the youngest of 6 children. Two died in infancy of unknown diseases. Questioning of the mother concerning the other children for any urologic symptoms yielded a negative answer. The mother was in good health but the father was suffering from pulmonary tuberculosis.

Physical examination on admission to the hospital revealed a fairly developed and well-nourished, but pale, very irritable child. The temperature was 102.4° F. rectally, the pulse 100 per minute, the respirations 27 per minute, and the weight 19 pounds and 4 ounces. The blood pressure was 82/42 mm. Hg. The heart and lungs were normal. The abdomen was soft, and the liver and spleen were not enlarged. The suprapubic region was

From the Blanco Hospital.

slightly tender. The external genitalia were normal. The external urinary meatus appeared markedly inflamed and patulous. Crying of the child during the examinations resulted in the appearance of a thin bulging globular mass from the vagina (Fig. 1). Careful examination disclosed that this mass had projected through the urethra and was hardly compressible even under considerable pressure. Further examination of the mass failed to reveal evidence of ureteral orifice. No abnormalities were noted on examination of the lymphatic and skeletal systems. There were no abnormal reflexes, motor or sensory disturbances.

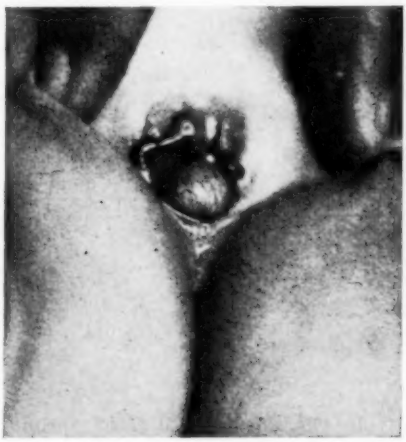

Fig. 1.—Smooth-walled vaginal mass projecting through the urethra. Engorged veins give the mass a superficial discoloration.

Laboratory studies were held to a minimum because of financial consideration. On admission, the hemoglobin was 78 per cent, the red blood count 4.4 million, and the white blood count 10,950 for each cubic millimeter of blood. The differential count showed 59 polymorphonuclears, 29 lymphocytes, 4 monocytes, 2 eosinophils, and 6 "stab" cells. The blood Wassermann and tuberculin test were negative. The blood urea nitrogen was 16 mg. per 100 c.c. The total serum protein and albumin-globulin ratio were within normal limits. The stool was negative.

The catheterized urine specimen was of turbid appearance, amber color, acid pH, specific gravity 1.022, and contained many pus cells. Culture of the catheterized urine grew out *Staphylococcus aureus*. Smears and cultures of the urine for acid-fast bacilli were negative.

In view of the above clinical data, a complete urologic investigation including intramuscular excretory urography, retrograde cystography, and cystourethroscopic examination was carried out.

Intramuscular excretory urography, using Diodrast mixed with hyaluronidase as contrast medium, injected into the soft tissues of both buttocks showed normal function of both kidneys. The right collecting system and ureter appeared normal. On the left, however, there was a moderate hydroureteronephrosis. Retrograde cystography disclosed in the anteroposterior and lateral views a filling defect in the base of the bladder (Figs. 2 and 3).

Cystourethroscopic examination demonstrated no urethral abnormality. The cystoscopic field was blocked and structures could not be identified properly despite overdistention of the bladder. Indigo carmine was injected intravenously and, although the dye could be seen in the bladder within 7 minutes, the point of entrance of the dye could not be determined.

No abnormal findings were noted in the roentgenographic examinations of the chest and long bones. Barium studies of the rectosigmoid were reported normal.

On the basis of the above findings it was felt that suprapubic exploration of the bladder was the method of approach. This advice was given to the family and was accepted.

Operation.—On Nov. 17, 1956, under open-drop ether anesthesia, a suprapubic midline incision was made. The incision was deepened downward to the urinary bladder while the rectus muscle was retracted laterally on

either side. As the bladder was opened, bulging folds of redundant mucous membrane presented throughout the extent of the trigone, especially near the bladder neck. The folds were thin walled and appeared to stem solely from the trigone. Indigo carmine intravenously administered appeared in good concentration from the right kidney in 4.5 minutes, but little dye was seen coming from the left ureteral orifice in 10 minutes and it did not become concentrated after 15 minutes. Both ureteral orifices appeared normal in shape and location and were entirely free from the redundant folds of trigonal mucosa. Except for a minimal inflammatory change around the left ureteral orifice, the rest of the bladder mucosa was normal.

As far as possible, all the redundant mucous membrane was very carefully excised and the bare area created was repaired with 3-0 chromic intestinal sutures. The pelvis was then explored for other anomalies but none was found. The incision was closed in layers after an indwelling No. 12 Foley bag urethral catheter was inserted.

Biopsy of the specimen removed from the bladder was reported as hypertrophic s m o o t h muscle fibers through which were scattered chronic inflammatory cells incorporated in dense fibrous tissue.

Postoperative Course.—Following surgery, the child had a satisfactory convalescence. Small oral feedings were retained. She was given antibiotics and intravenous fluids for 2 days. The urethral catheter was removed on the seventh postoperative day. The patient was discharged after 13 days' stay in the hospital.

Fig. 2.

Fig. 3.

Figs. 2 and 3.—Frontal and lateral views of preoperative retrograde cystogram clearly showing filling defect in base of bladder.

Periodic follow-up examinations disclosed no recurrence of the mass. She continued to improve and to recover the ground in her growth and development. A repeat intramuscular urography and retrograde cystography 8 months postoperatively showed the left hydronephrosis to have regressed and the bladder to fill almost normally (Fig. 4). The child was completely asymptomatic and her urine was essentially negative when last seen on Sept. 15, 1957, ten months after surgery.

COMMENT

It is noteworthy that, following an intensive search of the available literature, examples of redundant trigonal mucosa were found but in none of them did the mucosa protrude beyond the vesical neck. In our case the mode of presentation was unique in that the

Fig. 4.—Lateral view of postoperative retrograde cystogram showing almost normal filling of bladder.

redundant trigonal mucosa actually herniated into the urethra, appearing as a single globular mass through the vagina with every urination. The etiology or precise mechanism accounting for this unusual phenomenon is unknown but seems to be on a congenital basis, with straining as a possible exciting factor. In support of the congenital origin of this rare condition, it may be well to review the normal development of the trigone. "Embryologically, the trigone, a rather specialized portion of the bladder, is thought to be derived from the mesonephric duct and is of mesodermal origin, whereas the remainder of the bladder arises from the cloaca and is of endodermal origin. The trigone further maintains its identity because of its separation from the deeper muscle layers of the bladder by interposition of loose areolar tissue that allows ready establishment of a line of cleavage."[8]

It is our feeling that there might have been a congenital weakness of the trigonal attachment to the underlying muscular tissue in our case. Weakness of this attachment could have resulted also from the inflammatory changes involving the trigone and causing it to prolapse with straining.

The left hydroureteronephrosis was most likely due to pressure on the left ureteral orifice by a nearby mucosal fold flapping over it and acting as a valve mechanism, or it could have been brought about by some degree of chronic obstruction at the internal vesical orifice by the prolapsing trigonal mucosa. This was borne out by the regression of the hydronephrosis following surgery without intervention on the ureteral orifice.

Of added interest was the fact that, although the urethra was very patulous preoperatively on account of its dilatation by the prolapsing trigonal mucosa, following surgery the child had a perfect control of urination.

SUMMARY

A case of prolapsing trigonal mucosa in an 11-month-old girl is presented. A review of the relevant medical literature available failed to divulge reference to another case of this sort in which redundant trigonal mucosa prolapsed through the external

urinary meatus. A possible explanation for the etiology is offered. Surgical correction was instituted in the form of suprapubic excision of the redundant trigonal mucosa. Prompt recovery following operation was achieved.

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Those Were the Days

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AN ADVERTISEMENT IN THE BOSTON MEDICAL AND SURGICAL JOURNAL, FEBRUARY 4, 1858.

PROGNOSIS IN LEGG-PERTHES DISEASE

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A TOTAL of two hundred and eight cases of Legg-Perthes disease were studied to determine the factors of prognostic importance which might aid in the management of this condition.

Legg[5] believed, in 1916, that two distinct forms of this disease could be expected since a circulatory disturbance to the head of the femur formed its etiological basis. He theorized a "cap" type of involvement due to occlusion of blood vessels to the head of the femur at points only and a "mushroom" variety, which was thought to result from a generalized disturbance in circulation. He[6] later wrote (1927), "I have been struck by the fact that there are different types of end results and that they bear a definite relationship to the different types of the original pathology. In other words, it is possible to prognosticate the ultimate change in structure and to some extent the functional disability at an early age in the course." The "mushroom" label was applied to those hips which had uniformly less severe involvement with a better prognosis. The "cap" type exhibited fragmentation with occasional complete disappearance of the head, neck involvement, pathological changes of much longer duration, and a much poorer prognosis.

Eyre-Brook[2] maintained that the type of involvement, the age of the patient, the duration of the disease before treatment, and the efficiency of the treatment were related to the result. He found that the natural course of the disease was more severe after the age of 7 years.

Levy and Girard[7] wrote that results depended on how early treatment was begun and the type of treatment.

Heyman and Herndon[4] observed that the marked individual differences which existed in the disease process were probably the most important factors influencing the end result and that the age of the patient was related to the severity of involvement. With few exceptions, their cases illustrated that better results could be expected in the younger patients. The latter observation was confirmed by Mindell and Sherman[8] and by Pederson and McCarroll.[9]

While the earliest writers on the subject such as Legg believed that treatment did not influence the outcome, it has been effectively shown that some form of protection from

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weight-bearing until regeneration of the head is well advanced leads to less deformity in the majority of cases. The observation has also been recorded in recent years[1, 3, 4] that, once regeneration is well under way, further collapse of the head is rare even though unprotected weight-bearing is allowed. Ultimate function and disability are directly proportional to the severity of deformity left by the disease process.[1]

The material for this study was obtained from 208 cases.

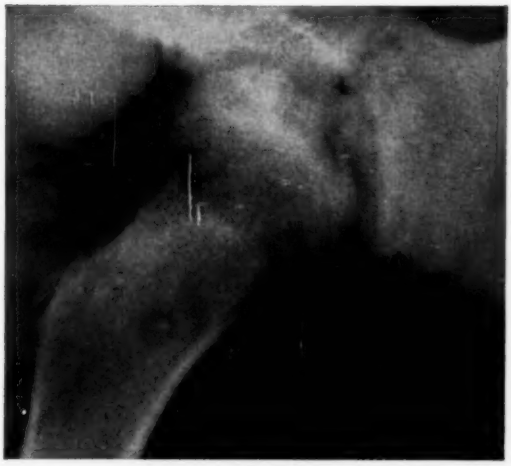
Fig. 1.—Case 1. *A*, Aug. 28, 1940; *B*, Sept. 30, 1940; *C*, Jan. 27, 1942; *D*, Aug. 23, 1950.

Age Distribution.—In 200 cases the age when the patient was first seen ranged from 2.8 to 14 years as follows: 2.8 to 5 years, 66 cases or 33 per cent of total; 6 to 9 years, 100 cases or 50 per cent of total; 10 to 14 years, 34 cases or 17 per cent of total.

Sex Incidence.—The sex incidence in 208 cases was: male, 166 cases or 79.8 per cent of total; female, 42 cases or 20.2 per cent of total.

Fig. 2.—Case 2. *A*, July 25, 1952; *B*, April 29, 1953; *C*, Feb. 19, 1954; *D*, Feb. 15, 1955.

Fig. 3.—Case 3. *A*, Oct. 11, 1951; *B*, Sept. 28, 1951; *C*, June 4, 1952; *D*, Aug. 5, 1953; *E*, Sept. 29, 1954; *F*, Oct. 5, 1955.



E.

F.

Fig. 3. *E* and *F*.

Side Involved.—In 207 cases the side involved was: right, 96 cases or 46.4 per cent of total; left, 84 cases or 40.6 per cent of total; bilateral, 27 cases or 13 per cent of total. (It is interesting to note that half of the bilateral cases occurred in the youngest age group: 2.8 to 5 years.)

Basis of Evaluation.—Heyman and Herndon's[4] "comprehensive quotient" was employed throughout to measure the result in each hip at follow-up or when regeneration of the head of the femur was complete or almost complete. In bilateral cases, average figures obtained by measuring seventy normal hips were used as the basis of comparison. The comprehensive quotients from the study were then tabulated to calculate the prognostic importance of the following factors: (1) status of progression of the disease process on roentgenogram when patient was first seen; (2) severity of involvement; (3) age at the beginning of treatment; (4) type of conservative treatment.

The ratings were:

90 to 100 per cent of normal = excellent.
80 to 89 per cent of normal = good.
70 to 79 per cent of normal = fair.
under 70 per cent of normal = poor.

ILLUSTRATIVE CASES

The illustrative cases are given in increasing order of severity of involvement.

CASE 1.—C. S., aged 6.8 years. Duration of symptoms was one month. There was the mildest type of involvement with the central portion only of the head affected. Treatment, begun in an early stage of the disease, consisted of bed rest with and without traction for twenty-one months followed by three months of ambulatory nonweight-bearing and then six months more of bed rest. The comprehensive quotient was 96.6 per cent. The result was excellent. (Fig. 1.)

CASE 2.—D. J., aged 5.5 years. Duration of symptoms was one month. There was a mild type of involvement with more of the central portion and surface of the head affected than in Case 1. Treatment, begun early, consisted of a suspension sling and crutches for nineteen months. Comprehensive quotient was 92.2 per cent. Result was excellent. (Fig. 2.)

Fig. 4.—Case 4. *A*, July 16, 1940; *B*, April 28, 1941; *C*, Sept. 1, 1944.

Cases 1 and 2 demonstrate the mildest varieties of involvement with an excellent prognosis, generally found in younger children. The few untreated cases with excellent results belonged to this group.

CASE 3.—T. C., aged 10 years. Duration of symptoms was one month.

There was a severe grade of involvement including mainly the superior lateral three-fifths of the head. Treatment, begun in the very early stage, consisted of a suspension sling and crutches for thirty-two months. Comprehensive quotient was 86.6 per cent. Result was good. (Fig. 3.)

Comprehensive quotient was 88.3 per cent. Result was good. (Fig. 4.)

CASE 5.—F. VN, aged 7 years. Duration of symptoms was six months. There was severe involvement of entire head and adjacent neck. Treatment, begun in early stage, consisted of bed rest with traction for nine

Fig. 5.—Case 5. *A*, Sept. 20, 1946; *B*, April 10, 1947; *C*, July 29, 1948.

CASE 4.—S. F., aged 5.5 years. Duration of symptoms was three months. There was severe involvement, including some of the head and adjacent neck. Treatment, begun early, consisted of bed rest with and without traction for thirty-four months followed by an ischial weight-bearing brace with a shoe elevation on the opposite side for thirteen months.

months, followed by a suspension sling and crutches, for nine more months. Comprehensive quotient was 63.2 per cent. Result was poor. (Fig. 5.)

CASE 6.—L. H., aged 11 years. Duration of symptoms was two months. Treatment, begun in an early stage, consisted of five months of bed rest

followed by nine months in a suspension sling with crutches. This most severe variety of involvement, with a very poor prognosis, is typical of the older age group. The entire bony head, which never quite absorbs, and the neck in patients such as this rapidly flatten and progress to severe deformity in spite of complete protection from weight-bearing in any form (including a plaster spica). Comprehensive quotient was 50.1 per cent. Result was poor. (Fig. 6.)

Fig. 6.—Case 6. *A*, Jan. 26, 1953; *B*, Aug. 14, 1953; *C*, May 15, 1956.

STATUS OF PROGRESSION OF THE DISEASE ON ROENTGENOGRAM

Hips were classified as follows:

V. E. = Very early. Minimal porosis or sclerosis of the femoral head. Irregularity or mottling of the epiphyseal line. No appreciable loss in height of the femoral head.

E. = Early. Advanced sclerosis and/or porosis with minimal flattening or absorption of the femoral head. Minimal widening, if present, of the metaphysis.

A. = Advanced. The femoral head in various stages of disintegration.

V. A. = Very advanced. The regenerative process in the femoral head, well established.

Where treatment was begun early in the course of the disease, the

majority of hips, managed conservatively by protection from weight-bearing, gained excellent and good results. The instances of fair and poor results in cases treated early occurred in hips with severe involvement. On the other hand, a few cases with mild involvement, not treated until late, achieved excellent hips with little or no deformity. A small group of six cases which received no treatment and ten which

STATUS of PROGRESSION	RATING	NUMBER of HIPS	PERCENT
VE 30 HIPS	E	14	46.7
	G	11	36.7
	F	3	10.0
	P	2	6.6
E 79 HIPS	E	30	38.0
	G	25	31.7
	F	19	24.2
	P	5	6.1
A 52 HIPS	E	8	15.4
	G	19	36.5
	F	15	28.8
	P	10	19.3
VA 17 HIPS	E	2	11.8
	G	3	17.6
	F	8	47.1
	P	4	23.5

Chart I.—Relationship between status of progression of the disease process on roentgenogram when first seen and the result (based on the measured comprehensive quotient at the termination of the active treatment period)—178 hips.

AGE GROUP	SEVERITY	NUMBER of HIPS	PERCENT
2.8 to 5 YEARS	MILD	37	63.8
58 HIPS	SEVERE	21	36.2
6 to 9 YEARS	MILD	39	47.6
82 HIPS	SEVERE	43	52.4
10 to 14 YEARS	MILD	12	41.4
29 HIPS	SEVERE	17	58.6

Chart II.—Relationship between age at beginning of treatment and severity of involvement—169 hips.

were treated operatively by drilling from within out had the poorest results.

The amount of femoral head involved was found to range from a small portion (usually the superior-lateral aspect) to the entire head and adjacent neck of the femur. For relative

SEVERITY	RATING	NUMBER of HIPS	PERCENT
MILD 89 HIPS	E	42	47.2
	G	34	38.2
	F	11	12.4
	P	2	2.2
SEVERE 81 HIPS	E	10	12.3
	G	29	35.8
	F	25	30.9
	P	17	21.0

Chart III.—Relationship between severity of involvement and the result (based on the measured comprehensive quotient at the termination of the active treatment period)—170 hips.

AGE GROUP	RATING	NUMBER of HIPS	PERCENT
2.8 to 5 YEARS 69 HIPS	E	34	49.3
	G	21	30.4
	F	10	14.5
	P	4	5.8
6 to 9 YEARS 102 HIPS	E	25	24.5
	G	33	32.3
	F	32	31.4
	P	12	11.8
10 to 14 YEARS 29 HIPS	E	1	3.5
	G	11	37.9
	F	9	31.0
	P	8	27.6

Chart IV.—Relationship between age at beginning of treatment and the result (based on the measured comprehensive quotient at the termination of the active treatment period)—200 hips.

The severity of the disease process in the individual case varies greatly.

classification purposes, the hips were divided into the following broad groups.

1. *Mild Involvement.*—In this group, hips with any or all of the following were included: (a) necrosis of only a portion of the femoral head (less than half); (b) minor or no involvement of the adjacent metaphysis; (c) simultaneous progression of the processes of disintegration and regeneration of small portions of the bony head.

tain. The history given by the parents, in many cases, was vague. Some cases of mild involvement progressed with very mild transient symptoms or none at all. No attempt was made to determine the age of onset. Thus, the determinations in this study were calculated from the time the disease was noted and treatment begun.

While, in many cases, the severity can be determined from the first roentgenogram, in others this factor does not become evident until later

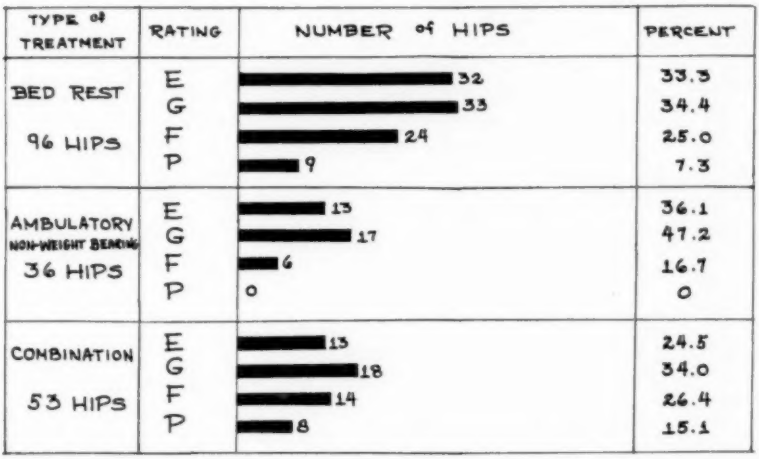


Chart V.—Relationship between type of conservative treatment and the result (based on the measured comprehensive quotient at the termination of the active treatment period) —185 hips.

2. *Severe Involvement.*—Included in this group were hips with any or all of the following: (a) total or almost total necrosis of the head of the femur; (b) marked involvement of the adjacent metaphysis; (c) almost complete disappearance of the bony head before regeneration; (d) tendency to fairly rapid flattening and deformity in spite of treatment.

The age of onset of the disease itself is extremely difficult to ascer-

in the disease. Younger children, for the most part, tended to have less severe involvement, with a better prognosis. A few cases of mild involvement in the youngest age group, which had progressed asymptomatically and were discovered by accident in an advanced stage of the disease, had excellent results. With few exceptions, in the younger children with mild involvement treated early

excellent or good results were obtained. Older children tended to more severe involvement with a poorer prognosis, even in some treated by complete rest in bed, traction, or a plaster spica, at a very early stage in the disease.

The amount of deformity left in the wake of the disease was influenced more by the severity of involvement and status of progression when treatment was begun than it was by the specific type of nonweight-bearing employed. Total bed rest with or without traction showed no advantage over the ambulatory methods such as the caliper patten ischial weight-bearing brace with a three and one-half inch cork shoe elevation on the opposite side or a suspension sling and crutches. Children treated on an ambulatory basis seemed to make an excellent adjustment to their disability and were able to continue their regular schooling. They were active and happy. On the other hand, confinement to bed of these otherwise healthy children, who in many cases were displaced from their home and family environment into a convalescent home for periods ranging up to three years, led to many behavior problems. The unilateral atrophy present in the ambulatory cases at the completion of the treatment decreased progressively after beginning normal weight-bearing and was never a problem after a few years. Cases in which one-third or more of the treatment time was divided between ambulatory and nonambulatory methods were classified in the combination group. Many of the latter were started on one method and converted back and forth to others due to family pressure or an unfavorable roentgenogram. There was a greater proportion of hips with severe involvement in this group than in either the ambulatory or bed rest groups; consequently, the results proved less favorable. The relative number of cases of mild or severe involvement and the number treated early or late were approximately equal in the bed rest and ambulatory groups.

Bilateral cases in which the first hip was treated on an ambulatory basis showed no more tendency to poor results on the opposite side than did those in which the first hip had been treated on bed rest.

With the exception of simultaneous bilateral involvement, the ambulatory nonweight-bearing methods of treatment appear to be more advantageous.

SUMMARY AND CONCLUSIONS

1. Two hundred and eight cases of Legg-Perthes disease have been studied to determine factors of prognostic significance.

2. The age of the patient, severity of involvement, and the status of progression of the disease when treatment was begun have been found to exert a direct influence on the end result. The younger patient with less severe involvement treated early in the disease has an excellent prognosis. The prognosis becomes less favorable with more severe involvement or when treatment is not started until later in the disease process.

3. Since complete bed rest with or without traction achieves no better results than the ambulatory nonweight-bearing methods, the latter are preferable except in cases of bilateral simultaneous involvement.

4. Previous study[1] has shown that ultimate degenerative changes and disability are directly related to the severity of deformity caused by this disease. Only the hips with excellent results may be expected to go through life without further difficulty from this source.

The generosity of the staffs of the Alfred I. duPont Institute, Wilmington, Delaware, the Hospital for Joint Diseases, New York, New York, and The Children's Seashore House (including cases referred from the Hospital of the University of Pennsylvania), Atlantic City, New Jersey, in permitting study of their cases is gratefully acknowledged. The author wishes to express his gratitude to Mr. Alton Shader who helped compute the data from cases at the Alfred I. duPont Institute.

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Among the committees appointed at the annual meeting of the American Medical Association in 1858 were:

1. *Special Committee on the Microscope.*—Drs. Holsten of Ohio, Dalton of New York, Hutchinson of Indiana, Stout of California, and Ellis of Massachusetts.

2. *Committee on Diseases and Mortality of Boarding Schools.*—Dr. C. P. Mallengly, of Kentucky, chairman.

3. *Committee on Milk Sickness.*—Dr. Edward A. Murphy of St. Louis, chairman.

FROM THE BOSTON MEDICAL AND SURGICAL JOURNAL, 1858.

CALCULATION OF NUTRITIONAL ALLOWANCES FOR INFANTS AND CHILDREN ON THE BASIS OF BODY SURFACE

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IN RECENT years, the calculation of parenteral fluid requirements and drug dosages according to surface area has become a common pediatric practice.[1, 2] Body surface was found to be a better reference system for the growing child than body weight. Fluid and electrolyte needs for parenteral therapy as well as drug dosages could be expressed in single figures per square meter of body surface rather than in a multitude of figures per weight units varying for different age groups. It seems reasonable to try to relate nutritional allowances of infants and children to body suface area also.

In the past, many methods have been used to calculate appropriate infant feedings. A "common sense" attitude has now replaced former rigidity and we think more in terms of dietary allowances than in terms of requirements, and within certain bounds we permit each infant and child to choose his own intake.

But there are certain situations in which a precise formulation of diet is necessary. During gavage feeding, in metabolic balance studies, and when a strict dietary regimen is being used in the management of diabetic children, one must prescribe fixed amounts of total calories, protein, fat, and carbohydrate. At present we rely mainly on extensive tabulations that outline the daily requirements of these things for various age groups.

However, it would seem more convenient to have available single figures that would be applicable to all age groups. In view of this, an attempt was made to correlate caloric allowances with body surface area. A linear relationship between these two variables was found, and simple figures for caloric needs for the normally growing and active child per square meter of body surface were derived.

METHODS

1. To determine average surface areas for certain age groups, the data from the "Studies of Child Health and Development" of the Harvard School of Public Health were utilized for children up to and including the age of 4 years, and from the Iowa Welfare Research for children from 5 to 15 years old inclusive.[3] The figures for the 50-percentile groups for weight and height in each age group were used to calculate the "50-percentile body surface" according to nomograms derived from DuBois' formula.

2. For each age group the daily caloric allowances for infants and children were calculated for the 50-percentile weights of each age group according to the data accumulated in the United Kingdom, Canada, and the

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United States[4] representing adequate caloric allowances.

3. The values obtained under paragraph 1 for the "50-percentile surfaces" were plotted on the ordinate and the values for dietary allowances on the abscissa of the figure.

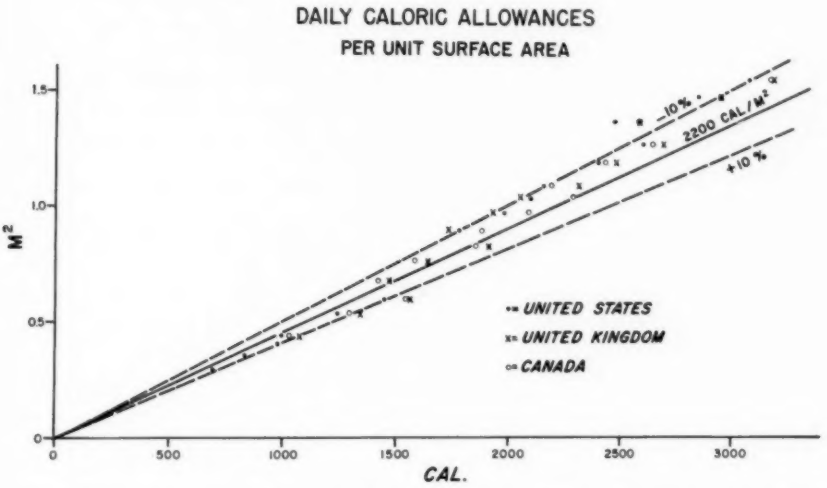

Fig. 1.—Correlation between estimated dietary allowances (United States, United Kingdom and Canada) and "50-percentile surface areas" of children up to and including the age of 15 years.

RESULTS

A linear relationship was found between the "50-percentile surface areas" and caloric allowances for all age groups from 1 month to 12 years inclusive. Since each individual value was thought to be somewhat arbitrary, no actual regression line was calculated. A caloric need of 2,200 calories per square meter appeared to be a close approximation. Allowing a variation of ± 10 per cent, the majority of values lie within this range. Only for children of the ages 13 to 15 inclusive, the recommended values are slightly lower than 2,200 calories per square meter.

COMMENT

The advantage of knowing caloric requirements per square meter of surface area is that only one figure needs to be remembered, 2,200 calories. Caloric needs for all pediatric age groups can be calculated on the basis of this alone. We can also establish allowances of protein, carbohydrate, and fat, using this reference standard. Assuming that 15 per cent of the caloric intake should be represented by protein, 80 Gm. per square meter is an appropriate figure for that substance (15 per cent of 2,200 = 330 calories, which is supplied by 80 Gm. of protein). Taking 50 per cent as the corresponding figure for carbohydrate, we can set 265 Gm. per square meter as the proper amount (50 per cent of 2,200 = 1,100 calories, which is supplied by 265 Gm. of carbohydrate). Eighty-five grams per square meter is a reasonable figure for fat allowance,

if one accepts 35 per cent as a good percentage of the caloric intake to be represented by that foodstuff (35 per cent of 2,200 = 770 calories, which is supplied by 85 Gm. of fat). The inactive child will probably need 25 per cent fewer calories.

One might object to the procedure of determining the surface area of each child. However, heights or lengths as well as weights should be routinely obtained anyway, and with this information it is very simple to read off surface areas from a readily available nomogram.

The main disadvantage is that the linear relationship between dietary allowances and body surface does not extend beyond the age of 12 years and it certainly does not continue into adult life. For children of ages 13 to 15 years, a value of 2,000 calories per square meter appears to be more nearly correct (figure). No data are available to test the relationship between surface area and caloric allowances in premature infants.

SUMMARY

A linear relationship between caloric allowances and body surface area was found for the pediatric age group. The caloric need of a normally active, growing child approximates 2,200 calories per square meter. In terms of specific foodstuffs, this need would be met by 80 Gm. of protein, 265 Gm. of carbohydrate and 85 Gm. of fat, per square meter of body surface.

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EDUCATION OF CEREBRAL PALSIED CHILDREN

The Role of Meprobamate: A Preliminary Evaluation

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EDUCATION of children with cerebral palsy must include some means of reduction of spastic or involuntary movements.[1, 2] Until some measure of control is attained over purposeless body movement, scholastic achievement will be fragmentary. However, muscle relaxation alone bears no direct relation to intellectual or emotional stability. Equally vital to education is control of anxiety, emotional tension, and behavioral aberration—all common symptoms among brain-damaged children.[3-5]

Of the muscle relaxants available to date, meprobamate is reported also capable of relieving anxiety and emotional tension. The drug acts on the central nervous system without disturbing autonomic functions.[6] Several investigators have reported meprobamate efficacious in treatment of cerebral palsy.[2, 7, 8, 9] Kugelmass[10] has found the drug to control partially or completely various behavioral disturbances, including those commonly associated with cerebral palsy.

The intent in this study was to ascertain whether meprobamate could directly or indirectly influence the ability of cerebral palsied students to learn.

STUDY CONDITIONS

Twin Falls, Idaho, Cerebral Palsy School is a branch of the community's public school system. Enrollment is restricted to handicapped children with symptoms referrable to brain lesions. The school came into being six years ago to answer the scholastic needs of educable cerebral palsied children in the area. The local Board of Education furnishes two teachers and appropriate school supplies. Parents and local service groups support the project's therapeutic needs, including the services twice weekly of a qualified physical therapist.

The school functions primarily to supply academic instruction. It is only secondarily a physical therapy or rehabilitation center.

Of 19 patients enrolled, 10 children with cerebral palsy were selected for inclusion in the study. All 10 patients had received academic instruction and undergone evaluation for at least two years prior to the study. Age ranged from 5 to 24 years. All 10 patients could sit upright for varying periods, although 3 required mechanical support. Two patients were confined to wheel chairs. The others were ambulatory: 4 could walk without aids, 3 with braces and a supporting arm, and 1 with a caster-mounted walker and duckshoes.

Intellect ranged from normal to low (less than IQ 60, Terman-Binet Scale). Five patients could not read. The remaining 5 had varied abilities to read.

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TABLE I. PROTOCOL OF TEN CEREBRAL PALSIED

PATIENT NO.	1	2	3	4
INITIALS	R. R.	E. D.	L. N.	M. McL.
DATE BORN	April 1, 1952	April 15, 1948	April 21, 1947	May 6, 1944
AGE (YEARS)	5	9	10	13
DIAGNOSIS	Spastic	Athetotic, tension with spasticity	Spastic	Athetotic with spasticity
DEGREE	Mild	Moderately severe	Moderate	Severe
INVOLVEMENT	Hemiplegia	Quadriplegia	Quadriplegia, esp. lower extremities	Quadriplegia
SEIZURES	Occasional grand mal on diphenylhydantoin sodium	None	Occasional petit mal	Occasional grand mal, partially controlled with Mysoline
SPEECH	Stutters	Good	Fair	Very poor
INTELLECT (EST.)	Normal	Good	Low-normal	Low-normal
AMBULATION	Walks	Braces and person to help	Walks with walker and duckshoes	Walks with braces and person to help
HEARING	Normal	Normal	Normal	Normal
EYESIGHT	Normal	Normal	Normal with glasses	Normal
DENTITION	Normal	Corrected to normal	Normal	Under correction to normal
BEHAVIOR	Mildly disturbed	Normal	Mildly disturbed	Moderately disturbed
PROBABLE ETIOLOGY	Birth (bleeding and cramping in late pregnancy)	Kernicterus, secondary to RH incompatibility, prematurity	Neonatal anoxia (prolonged labor, heavy maternal sedation)	Neonatal anoxia (difficult labor)
YEARS UNDER OBSERVATION PRIOR TO STUDY	2	4	2	4

One could read only while the instructor traced the page, line by line. Without the instructor's guiding finger, the other readers often lost their place due to spastic or involuntary movements jerking their eyes from the printed page.

Before beginning the study all patients had been under the care of private physicians and dental practitioners. All children were physically healthy, considering the nature of their disability. Hearing was normal in all cases. Eyesight was normal or corrected to normal. Dentition was normal or slightly abnormal with correction of all remedial defects. Table I lists diagnoses and other pertinent information.

The 80-week study began in September, 1956. Base-line responses were established in the first six weeks,

PATIENTS RECEIVING MEPROBAMATE THERAPY

5	6	7	8	9	10
F.C.	D. K.	P. B.	N. S.	N. T.	B. F.
May 1[illegible], 1943	April 4, 1941	Dec. 25, 1937	Sept. 3, 1936	June 4, 1933	Dec. 7, 1933
14	16	20	21	24	24
Athetotic, tension	Spastic	Athetotic, tension with spasticity	Athetotic with spasticity	Spastic	Athetotic, tension with spasticity
Mild	Severe	Moderately severe	Mild	Severe	Severe
Tremor of upper extremities	Quadriplegia	Hemiplegia	Quadriplegia	Quadriplegia	Quadriplegia
None	None	None	None	None	None
None	None	Fair	Good	Fair (intelligible to family)	None intelligible
Low	Low	Low-normal	Low-normal	Normal	Good
Walks	Walks with braces, walker, and person to help	Walks	Walks	Confined to chair	Confined to chair
Normal	Normal	Normal	Normal	Normal	Normal
Normal	Normal	Normal with glasses	Normal with glasses	Normal	Normal
Normal	Normal	Normal	Corrected to normal	Normal	Normal
Normal	Moderately disturbed	Normal	Moderately disturbed	Normal	Normal
Neonatal anoxia (prolonged, difficult labor). Birth wt., 10 lb. 14 oz.	Neonatal anoxia (prolonged labor)	Birth	Neonatal anoxia (difficult labor)	Neonatal anoxia	Encephalitis at age 3½ years
4	4	2	4	4	4

and compared with those noted in prior years. Enrollment, daily school schedule, teaching techniques, staff personnel, and other controllable factors remained stable during the study.

MEDICATION

Meprobamate* was administered to 10 of 19 students under the supervision of the school medical director. The drug was given by an instructor once daily and swallowed in her presence. Medication was omitted at first over week ends, during school holidays, and on days lost through illness. Later, in six cases, meprobamate was supplied at parental request to permit continuous therapy.

Dosage began at a low level. If no response became apparent after a

*Meprobamate (2-methyl-2-n-propyl-1,3-Propanediol dicarbamate) is available from Wyeth Laboratories, Philadelphia, Pa., as Equanil.

TABLE II. COMPARATIVE RESPONSE TO MEPROBAMATE THERAPY AT VARIOUS DOSAGE LEVELS

PATIENT NO. AND INITIALS	1 R. R.				2 E. D.							3 L. N.			4 M. McL.				5 F. C.			
MEPROBAMATE DOSAGE (MG. DAY)	0	400	0	400	0	400	600	0	600†	0	600†	0	200	400	0	400	800	0	400	800		
DURATION OF THERAPY (WEEKS, CUMULATIVE)	6 6	29 35	17 52	28 80	6 6	2 8	10 18	4 22	13 35	17 52	28 80	6 6	2 8	10 18‡	6 6	2 8	27 35	17 52	2 8	27 35		
ATTENTION SPAN	0	1	0	1	1	1	2	1	2	1	2	1	1	0	0	0	4	0	1	3		
ABILITY TO LEARN	0	1	0	1	1	0	2	1	2	1	2	1	1	1	0	0	4	0	1	2		
OUTLOOK ATTITUDE	0	2	0	2	4	4	4	4	4	4	4	1	1	1	0	0	4	0	1	4		
EASE OF HANDLING	0	3	0	3	1	1	4	1	4	1	4	1	1	1	0	0	4	0	1	2		
MUSCLE RELAXATION	0	0	0	0	1	1	3	1	3	1	3	1	1	1	0	0	3	0	1	2		
INVOLUNTARY MOVEMENTS	0	0	0	0	1	1	3	1	3	1	3	1	1	1	0	0	3	0	1	3		
ENDURANCE	0	2	0	2	1	1	2	1	2	1	2	1	1	2	0	0	2	0	1	1		
BLOOD TESTS‖	Negative				Negative							Negative			Negative				Negative			
URINALYSIS‖	Negative				Negative							Negative			Negative				Negative			
REMARKS					No improvement at lower dosage							No effect at lower dosage			No effect at lower dosage				No effect at lower dosage			
	Far easier to handle; less hot-tempered				Seemed too relaxed at first, could no longer sit to eat. Two hundred milligrams added at bedtime: improved sleeping habits. Great improvement for physical therapy. Easier to handle and to install braces							Variable performance without medication. Under therapy appeared worried, apprehensive			Formerly lazy, belligerent, uncooperative. Now cooperative, willing to try. More acceptable and pleasing personality				Less tense, pier, less or, was please. patient tirely socially table p ality			
	Able to read for first time											On medication became somewhat giggly, less serious in class. After drug withdrawal, patient tended to cry more easily when pushed to perform			More school progress in first four months of therapy than in prior two years. Able to read for first time				Progress by low lect			
	Parents requested drug continuance				Parents requested drug continuance										Parents requested drug continuance				Parents drug tinuan			

Response Code: 0 = Severely deficient; 1 = moderately deficient; 2 = slightly deficient; 3 = approaching normalcy; 4 = normal for age level.

*Study initiated in September, 1956. Drug first administered in November, 1956, continued through May, 1957, discontinued during summer vacation (except in Cases 6, 7 and 10), resumed in September, 1957.

†200 mg. at bedtime.

‡Drug

‖Blood

¶Respo and agi

VARIOUS DOSAGE LEVELS AMONG TEN CEREBRAL PALSIED PATIENTS TREATED FOR 1.5 YEARS*¶

	5 F. C.				6 D. K.		7 P. B.			8 N. S.					9 N. T.						10 B. F.				
	400	800	0	800	0	400	0	400	800§	0	400	800	0	800	0	600	800	1200	0	1200	0	600	1000	1200	1600
	2	27	17	28	6	72§	6	2	72	6	2	27	17	28	6	2	2	25	17	28	6	2	2	2	72§
	8	35	52	80	6	80	6	8	80	6	8	35	52	80	6	8	10	35	52	80	6	8	10	12	80
	1	3	1	3	0	3	1	1	2	1	1	2	1	2	4	4	4	4	4	4	4	4	4	4	4
	1	2	1	2	0	2	1	1	2	1	1	2	1	2	4	4	4	4	4	4	4	4	4	4	4
	1	4	1	4	0	3	1	1	4	1	1	3	1	3	3	3	3	4	3	4	3	3	3	3	4
	1	2	1	2	0	3	1	1	2	1	1	4	1	4	0	0	0	1	0	1	1	1	1	1	3
	1	2	1	2	0	3	1	1	3	1	1	3	1	3	0	0	0	1	0	0	0	0	0	0	2
	1	3	1	3	0	2	1	1	3	1	1	3	1	3	0	0	0	0	0	0	0	0	0	0	3
	1	1	1	1	0	3	1	1	3	1	1	2	1	2	4	4	4	4	4	4	2	2	2	2	3
	Negative				Negative		Negative			Negative					Negative						Negative				
	Negative				Negative		Negative			Negative					Negative						Negative				
	No effect at lower dosage				No effect at lower dosage		No effect at lower dosage			No effect at lower dosage					No effect at lower dosage						No effect at lower drug dosage				
	Less tense, happier, less tremor, wants to please. Gave patient an entirely new and socially acceptable personality				Willing to try; improved endurance with walker and braces. Easier to handle. Better sleep pattern. Required less care at night		Happier, less morbid. Less awkward. Less breakage			Reduced nervousness, lessened mannerisms of fidgeting, doodling, nail biting					Reduced worry and apprehension over trivial home matters. Better sleep pattern						Easier to handle at home. No longer exhausts self in purposeless movements				
	Progress limited by low intellect				Less irritable, less crying, more able to work		Progress limited by low intellect; but better attitude, more desire to learn								Able to read, using a page-turning device						Before medication, could not sit through school day without exhaustion. Now can do so. Able to read, using page-turning device				
	Parents requested drug continuance						Parents requested drug continuance			Parents requested drug continance					Parents requested drug continuance						Parents requested drug continuance				

‡Drug discontinued on Jan. 22, 1957.
§Drug continued throughout summer vacation at parental request.
¶Blood tests and urinalysis performed twice.
*Responses at start of fall term, 1957, 52 weeks, may be lower than actual child status, due to excitation and agitation normally present in children at school opening.

minimum of two weeks' medication, dosage was increased. Lack of response following at least 14 additional days of observation brought increase to a second dosage plateau. Daily meprobamate intake was increased, plateau by plateau, until satisfactory response resulted.

Complete blood studies and urinalysis were performed after maximum dosage was reached, and once thereafter.

Medication was suspended over the summer vacation (i.e., after 35 weeks' observation) in all but Cases 6, 7 and 10. Administration of meprobamate was resumed in the fall, during the fifty-second week of the study, and has continued to date of this writing for a total of 80 weeks.

METHODS OF EVALUATION

Evaluation took place at two levels. First, ability of each cerebral palsied patient to follow the regular school program was tested. Second, change was noted in the physical status of each child.

Seven factors were considered at weekly intervals: (1) degree of muscle relaxation, (2) magnitude of spastic or involuntary movement, (3) ease of handling, (4) outlook and attitude, (5) endurance, (6) attention span, and (7) ability to learn. The medical director and physical therapist concerned themselves largely with the first four criteria. The two instructors observed the last four factors and related them to classroom performance. Evaluators did not compare results with one another until completion of the first phase of the study at 35 weeks.

Standards for evaluation of muscle relaxation, involuntary movements and ease of handling followed closely those defined by Gillette.[9] Criteria established by Millichap and Hadre[1] and by Wallace and associates[11] also were applied where practicable. Outlook and attitude were subjectively graded by all four evaluators. Endurance was a classroom comparison with previous observation of the child's ability to perform tasks without fatigue, and to continue through the school day without exhaustion. Attention span and ability to learn were estimated subjectively.

Response noted by evaluators was graded (after Gillette[9]) as follows: +1 = slight improvement in performance, +2 = fair improvement (less than 50 per cent), +3 = good improvement (50 to 75 per cent), +4 = excellent improvement (75 to 100 per cent).

The relatively stable nature of the study environment, and the known and consistent level of patient performance prior to therapy enabled use of each child as his own control. Table II expresses a composite of responses comparing prestudy performance with that while receiving meprobamate. Response to study conditions of the nine school children not receiving meprobamate indicated how successfully a stable environment was maintained.

REPORT OF CASES

Nine children who received no meprobamate continued to progress at the same retarded rate observed previously. Table II lists response of 10 children with cerebral palsy to varying doses of meprobamate.

In our series, patients responded to meprobamate only above a minimum

effective dosage level. Each child had a specific drug threshold: if less drug was given, not even muscle relaxation could be noted. At the proper dosage level, muscle relaxation and fewer spastic or involuntary movements occurred. Therapeutic response when it appeared did so within 3 to 7 days after dosage increase. No attempt was made to increase meprobamate dose beyond that necessary for response.

Patients became easier to handle as muscles relaxed and involuntary movements diminished. Response to physical therapy thereby improved. Where installing and adjusting braces was a 30-minute chore, it became a simple 5-minute task. Outer clothing was more easily donned and removed. Parents of cerebral palsied children were highly impressed by the often dramatic improvement in handling at home.

Incidence of emotional outbursts and aberrant behavior diminished. Sleep patterns improved, both at night and during school-hour naps. But even more interesting were the dramatic changes in behavior and attitude on attaining a therapeutic drug dose. On questioning, parents gave this last as the major reason for requesting drug continuance.

Increase in endurance was less obvious. Initially, in one patient, drowsiness in class obscured endurance increase. Yet as medication continued, students generally seemed less fatigued at the end of the school day than before the study. In some cases, increased endurance was reflected in greater alertness and more willingness to perform.

No doubt exists in the minds of instructors as to the decided increase in attention span and improved ability to learn. For at least two years previously, five students capable of reading at varied levels had been limited by muscle spasm and inability to concentrate. Between September, 1956, and June, 1957, the same five patients improved considerably in reading ability. Undoubtedly, improvement resulted in part from increased age. But the accelerated rate of reading progress was without precedent in school records and in the memories of instructors. Compared to previous school progress, the gain observed among these five patients far exceeded normal expectations.

The following case histories of typical improvement also demonstrate the need for individualization of the dosage in the cerebral palsied patient.

Case 1.—A 9-year-old male tension athetoid, with a neonatal history of kernicterus secondary to RH incompatability, was placed on 400 mg. of meprobamate daily in November, 1956. (See Tables I and II for supplementary information.) Response to physical therapy improved greatly in succeeding weeks. Ease of handling increased: previously, installation of braces was an exasperating 30-minute tussle; under medication, involuntary movements decreased considerably and made possible brace adjustment easily and in less than five minutes.

In spite of these gains, the patient became too sleepy under medication to perform scholastically at his known capacity. Meprobamate was discontinued on Jan. 22, 1957, since his academic progress could continue without the drug. Within 48 hours, athetotic symptoms reappeared.

A conference with his parents brought out that the child refused to go to bed until his parents retired, and that he watched television until 10 or

11 P.M. regularly. With this knowledge, another regimen of meprobamate was agreed on, correlated this time with the patient's need for a normal sleep pattern.

The patient received 400 mg. of meprobamate in one dose at school. Another 200 mg. was given between 8 and 9 P.M., and the child was put to bed immediately. With the aid of the drug, sleep ensued shortly and the child began to enjoy a full night's rest. As a result of improved sleeping habits, the patient's endurance increased beyond that existing prior to therapy, and he began to perform at full capacity in school. Desired muscle relaxation and diminution of involuntary movements returned under medication.

CASE 2.—This patient was a 13-year-old athetotic male whose symptoms were secondary to neonatal anoxia. Progress during his four years of academic instruction was greatly limited by his behavioral aberrations and negativistic attitude. He was belligerent to other students, antagonistic to instructors, and completely uncooperative.

After receiving 400 mg. of meprobamate daily for two weeks without noticeable effect, dose was increased to 800 mg. All observers were impressed by the rapid personality changes. Within 48 hours after increasing the dosage he became so quiet the instructors felt he must be ill. However, this improved attitude persisted as long as medication continued.

Currently, the student is interested, attentive, and cooperates willingly in both academic and physical instruction. He has attained primer reading level and has comparable gains in other subjects. Four years of prior instruction produced no academic results, whereas now the instructors feel the child holds considerable promise of learning. The parents report none of the old behavior problems and resistance in the home.

COMMENT

Subnormal ability to concentrate and consequential subnormal ability to learn are two basic problems confronting those entrusted with the education of cerebral palsied students. At times the very site of the disabling brain lesion limits teachability. More often, the spastic or involuntary movements seen in cerebral palsy frustrate the child's most sincere efforts to learn. The pupil who cannot control his motions sufficiently to keep his eye on a printed page or follow a line can hardly be expected to progress rapidly beyond a first-grade primer.

No direct influence of meprobamate on attention span or ability to learn can be proved from such a study as this. However, substantial improvement in academic progress did occur over the school year. This progress exceeded that anticipated from prior experience with the study group, and was felt to result from improved learning ability.

It is suggested that alleviation of muscle spasm and involuntary or spastic movements contributed to greater endurance, thus encouraging a longer attention span. Use of meprobamate modified and at the same time helped dispel anxiety and emotional tension. Consequently, classroom routine was disrupted less often. A better academic atmosphere resulted. Enhanced ability to learn came out of this improved environment and control of involuntary movements. Longer attention span and improved learning ability reflected themselves in better assimilation of information and faster school progress.

SUMMARY

In a relatively stable academic environment, 10 pupils with cerebral palsy received meprobamate to enhance their response to the school program. Therapeutic response appeared, in each successful case, only above a specific dosage level. Nine of 10 children under therapy completed the school year with increased attention span and improved ability to learn. Scholastic progress among these 9 was beyond that anticipated from earlier observation. In selected cases of cerebral palsy, meprobamate can encourage scholastic performance at maximum capacity, and can improve response to academic instruction.

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FERROUS SULFATE POISONING

Report of a Case Successfully Treated by Exchange Transfusion

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IRON poisoning in children has been reported with increasing frequency in recent years. Iron salts are often considered as innocuous drugs. However, it has been abundantly shown that the iron salts are not without danger to young children and sometimes may even prove fatal. Iron salts have been used for years without any regard to the fact that they might be toxic to children. Fatal cases may even have been misdiagnosed as infectious diarrheas or similar conditions. To compound the danger, in comparatively recent years iron salts have been dispensed in brightly colored tablets suggesting sugar-coated candies—an invitation to the unwary child. As few as 10 to 15 tablets have been reported as sufficient to cause death.[1]

The first case of poisoning with iron salts was reported from Great Britain in 1947 by Forbes.[2] Thomson[3] in 1950 reported six cases within a five-year period in one town. Spencer[4] in 1951 reported eight cases of iron poisoning, with four deaths. Since then, additional cases have been reported, each suggesting different methods of treatment.

In our case the usual treatment, including gastric lavage, cathartic, enema, oral administration of demulcents, infusion of electrolytes, and one dose of a chelating agent, was employed. In addition, the child had an exchange transfusion which we believe was lifesaving and contributed to the fast recovery.

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CASE REPORT

A white girl, 18 months old, was admitted to the Pediatric Service of the Elmhurst General Hospital at 9:30 A.M., Oct. 21, 1957, with a history of having ingested 15 to 25 Feosol tablets, two hours prior to admission. (Feosol tablet contains 3 grains of desiccated ferrous sulfate, the equivalent of approximately 5 grains of crystalline ferrous sulfate.) The patient was well developed and well nourished, with a normal birth history and in excellent health until the day of admission.

She had vomited for 30 minutes and passed several black watery stools. When first seen, she was very pale, cyanotic around the mouth, hands, and feet, and in a state of shock. Respirations were rapid, shallow, and irregular. Heart sounds were faint and rapid. Peripheral pulse was absent. Blood pressure was 55 systolic with 0 diastolic. Pupils were dilated and reacted sluggishly to light. Ears, nose, and throat were negative. Lungs were clear to percussion and auscultation. Abdomen was scaphoid, without palpable masses. The deep tendon reflexes were hypoactive. No pathological ankle reflexes were elicited. The patient was semicomatose.

General supportive therapy was instituted immediately. Oxygen, Lobeline, and Coramine were administered, the extremities were kept warm, and pharyngeal suction was used as indicated. Plasma was started, followed by 200 c.c. of whole blood. Gastric lavage with a saturated solution of sodium bicarbonate was done. The

gastric washings obtained were brownish with a few flecks of bright red blood. None of the tablets were recovered. After the lavage, 5 to 10 ounces of sodium bicarbonate solution was left in the stomach. Following these procedures, the patient's condition improved. However, she continued to show cyanosis of the lips, hands, and feet. Feedings consisted of eggnog and plain milk. In addition, she received 5 grains of bismuth subcarbonate, orally, every 4 hours.

On the afternoon of the day of admission, the temperature rose to 102° F. Penicillin was started. Versenate, 5.0 c.c. in 250 c.c. of 5 per cent dextrose in water, was given intravenously. By 4:00 P.M. of the same afternoon, the general condition was improved although cyanosis was still noted. It was then decided to do an exchange transfusion. A saphenous vein cutdown was performed and a polyethylene tube was inserted through the vein into the femoral vein for some 5 inches; 1,433 c.c. of blood was given in increments of 20 c.c. and the same amount was removed. The procedure was accomplished in 2 hours. Calcium gluconate was given, 2.0 c.c. for each 100 c.c. of blood introduced, to avert tetany. During the course of the exchange, the patient remained in a relatively good condition. Her color and general condition gradually improved and by the following morning she was markedly improved.

Laboratory findings were as follows: red blood cells 3,600,000; hemoglobin, 13.5 Gm.; hematocrit 33 per cent; white blood cells, 24,800 with 58 per cent segmental forms and 40 per cent lymphocytes; sedimentation rate, 3 mm. per hour. Urinalysis showed amber color, acid reaction, glucose and albumin negative with acetone, 1 plus, 10 to 12 white blood cells and 0 to 2 red blood cells. Stool was positive for occult blood.. Serum iron level was 3.5 mg. per cent. Serum electrolytes showed CO_2 combining power, 27 mEq., sodium 152 mEq., potassium 4.1 mEq., and chloride 112 mEq. Other findings were icteric index, 5 units; thymol turbidity, 1 plus; cephalin flocculation, 4 plus; albumin/globulin, 3.7/1.4; cholesterol/esters, 136/81. X-ray of chest was negative.

On the second hospital day the child was much improved. Color was good, temperature 100° F., and she retained fluids well. Tachycardia was still present and she continued to pass black watery stools. Improvement continued apace, and by the morning of the fourth day, she was fully recovered. Physical findings were completely normal. Gastrointestinal roentgenological study done on the sixth hospital day was negative. Patient was discharged after eight days of hospitalization.

DISCUSSION

It appears, on reviewing the literature, that most cases have occurred in children between 18 and 32 months of age. Symptoms may appear as early as 30 to 60 minutes after ingestion of the tablets. The severity of the symptoms is not necessarily related to the number of tablets ingested. Vomiting appears early, followed by drowsiness and pallor. Diarrhea and dehydration gradually lead to shock and coma. Hemorrhage, especially hematemesis, may occur early and sometimes be severe. Death may occur in 12 to 24 hours. A further feature that should be mentioned is a misleading period of clinical improvement preceding collapse, which has been observed in some fatal cases during the second 24-hour period. Death might sometimes occur up to 50 to 72 hours after ingestion of the tablets.

Spencer[4] believed that the vomiting, hematemesis, and collapse could be explained by the direct corrosive effect of iron salts on the stomach wall, and that death in the first few hours was due to shock. If the young patient survives the shock of the first stage, a deceiving improvement will be seen. Shortly after ingestion of the tablets, iron will be absorbed from the gastric

mucosa and upper jejunum. The level of circulating iron could reach 15 to 100 times the normal level. This amount of iron in the serum can cause a profound cell dysfunction. Necropsies have shown that the liver, spleen, kidney, lung, and brain have been variously affected. Some tissues may be damaged more than others. Involvement of the central nervous system is occasionally severe enough to cause death within the second and third 24-hour periods.

Recently, work has been done to clarify the effects of poisoning with the iron salts and the cause of death. Brown and Gray[5] in an excellent appraisal of the subject, together with a fine study of the pathological physiology, came to the conclusion "that, immediately after the ingestion and absorption of large amounts of iron, shock due to the presence of a circulating vasodepressant occurs; subsequently there is protein loss by destruction and renal discharge, and at the same time protein synthesis is depressed by liver necrosis and the effects of reticulo-endothelial block. The destruction of protein and loss of synthesis lead to a hypoproteinemia of varying degree accompanied by an alteration in amino acid metabolism, the latter manifested as a hepatic coma." Shorr and associates[6] demonstrated that ferritin was a vasodepressant, and Smith[7] considers that in iron poisoning excessive amounts of ferritin may be produced and released into the circulation, initiating and maintaining the vasomotor collapse characteristic of the early stages of iron poisoning. In any case, there is circulating in the serum a dangerously noxious substance which might produce a fatality quite quickly and unexpectedly. This unfortunate result might occur after a temporary improvement in the patient's condition following emergency shock therapy. This then was the rationale in performing the exchange transfusion—to remove this toxic substance from the circulation. The progress of the case justified the procedure. Exchange transfusions have been used to treat successfully cases of methyl salicylate poisoning[8] and boric acid poisoning.[9]

SUMMARY

A case of ferrous sulfate poisoning is reported in an 18-month-old child. In addition to the routine measures, the child received an exchange transfusion of 1,433 ml. of blood. The infant made an excellent recovery.

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INCARCERATION OF MECKEL'S DIVERTICULUM IN AN INGUINAL HERNIA

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ACCORDING to most necropsy reports, Meckel's diverticulum occurs in approximately 2 per cent of all persons. The embryology and anatomy have been completely reviewed in the literature and texts. The preponderance of cases in males is well known but poorly understood. This anomaly may give rise to serious complications which occur chiefly in the first and second decades of life. For this reason the pediatrician and the pediatric surgeon must maintain a high index of suspicion concerning this curious abnormality which can mimic so many conditions.

There are several very good general reviews of the complications of Meckel's diverticulum,[1-4] including hemorrhage, perforation, inflammation, obstruction, and intussusception. Moore and Parsons[5] reviewed neoplasms of this lesion. Calculi,[6] fishbones,[7] and other foreign bodies have been reported. Michael[8] reviewed tuberculosis. One very interesting report of a prenatal case with gangrene of the diverticulum at birth was presented by Chaffin.[1]

The purpose of this paper is to report a case of Meckel's diverticulum presenting as an inguinal hernia and to review the literature concerning this complication because the pediatric literature is essentially void of this subject.

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The opinions or assertions contained in this article are the private ones of the author and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

REPORT OF A CASE

A 4-week-old white boy was admitted to the U. S. Naval Hospital, Jacksonville, Florida, on Nov. 27, 1957, because his mother noted a fulness in his right scrotum the evening prior while changing his diaper. The "lump" increased in size and the baby became very fussy. Stools were normal and there had been no vomiting. Because of persistence of the mass, the parents brought the baby to the hospital at 3:00 A.M. Past history was noncontributory. Birth weight was 6 pounds.

On examination, he was a well-developed, well-nourished infant who appeared to be in no distress except that he cried loudly when his scrotum was manipulated. The vital signs were all normal. The weight was 7 pounds 8 ounces. Abnormal findings were limited to the genitalia. There was a right indirect inguinal hernia with a scrotal mass which was semitranslucent, firm, tender, and irreducible.

Laboratory studies showed a hemoglobin of 13.0 Gm. per 100 ml., and 11,150 white blood cells per cubic millimeter with a normal differential. Routine urinalysis was normal. Plain roentgenogram of the abdomen revealed no abnormality.

The initial hospital course included attempt to reduce the hernia, employing meperidine hydrochloride (Demerol), Trendelenburg position, and ice packs to the scrotum. The infant was placed on intravenous infusion of ½ strength saline and 2½ per cent dextrose in water. After attempting reduction of the hernia for 1½ hours, the surgeon was notified.*

*Surgery was performed by Peter S. Kroll, Captain (MC), USN.

The baby was prepared for surgery in the usual manner. An inguinal incision was made and a tiny hernia was reduced; however, a 3.0 cm. Meckel's diverticulum had entered the scrotum as a direct hernia. A right rectus incision was made, and the entire ileum was exposed for examination. The portions of ileum adjacent to the diverticulum appeared dark, as did the mesentery. Hot packs were applied to the compromised section of bowel, and after 30 minutes the integrity of the bowel returned. The diverticulum was excised, since no resection of ileum was required. The wound was closed in the usual manner, the baby was transfused with 40 ml. whole blood and returned to the ward. His postoperative course was uneventful and he was discharged in good condition, Dec. 10, 1957. Pathological report confirmed the diagnosis of Meckel's diverticulum without inflammation or heterotopic tissue. On outpatient examination one month after discharge, he seemed completely well. His right testis felt normal.

DISCUSSION AND REVIEW OF THE LITERATURE

The possibility of a diverticulum of the ileum presenting in an inguinal hernia is relatively rare, even though this possibility is mentioned in most textbooks of surgery. Watson,[9] in his exhaustive review of hernias in 1938, collected 96 cases where Meckel's diverticulum was found in an inguinal hernia. He stresses that, unlike other complications of Meckel's diverticulum, those presenting as an inguinal hernia are most rare in childhood. Since Watson's report, there have been several individual reports of isolated cases,[7-10-16] all in adults.

This rare complication in children must be kept in the pediatrician's mind, because the mildness and insidiousness of local symptoms may cause delay in surgical correction of strangulation.

SUMMARY

A most unusual complication of Meckel's diverticulum in childhood is presented, the literature is reviewed, and the importance of suspicion of this anomaly to further rapid surgical intervention is stressed.

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FAMILIAL DYSAUTONOMIA

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THE original description[1] and subsequent investigations of familial dysautonomia[2, 3] have led to the clarification of a most bizarre clinical syndrome. The rather peculiar pattern of signs and symptoms was found to be present when our patient was observed.

CASE REPORT

G. W., born Jan. 21, 1951, had a birth weight of 8 pounds 3 ounces. He suffered from colic and appeared to improve with the administration of goat's milk. Febrility had been marked with even minimal infections, and, on one occasion, a convulsion occurred with a temperature of 105° F., although elevation of temperature to this and even higher level on occasions was not accompanied by seizures. Respiratory infections had been noted on frequent occasions. The child had always evidenced a peculiar insensitivity to pain and tended to be dry-eyed on the rare occasions that he cried. Presence of corneal ulcer is questionable. The tendency to develop erythematous skin eruption had been slight and was related to excitement. Difficulty in writing, particularly in spacing, was noted when the child started to school. His work was of superior level in most respects.

The child had complained of abdominal (later localized as epigastric) pain during the year (1957) prior to his hospitalization and this discomfort was accompanied by profuse sweats, coldness in the hands and feet, and loss of appetite. Constipation and difficulty with passage of urine had been constant annoyances. An attack of severe arthritis in the patient's mother, which necessitated her hospitalization, had led to an exacerbation of the patient's symptoms several months before. Two weeks prior to hospitalization, the child suddenly fainted when he jumped from the bathtub. His temperature was recorded at 100° F., rectally, but soon dropped to a subnormal level.

Fig. 1.—Photograph of patient, G. W., showing awkward appearance, facies of apprehension, and scoliosis.

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Aided by a grant from the U.S. Public Health Service, National Institute of Neurologic Disease and Blindness (677D).

Vision and hearing were normal. The gag reflex was present. Blood pressure taken at rest was 102/65 mm. Hg.

bornness. Physical punishment was entirely without effect.

The patient's father had been treated for peptic ulcer, the mother

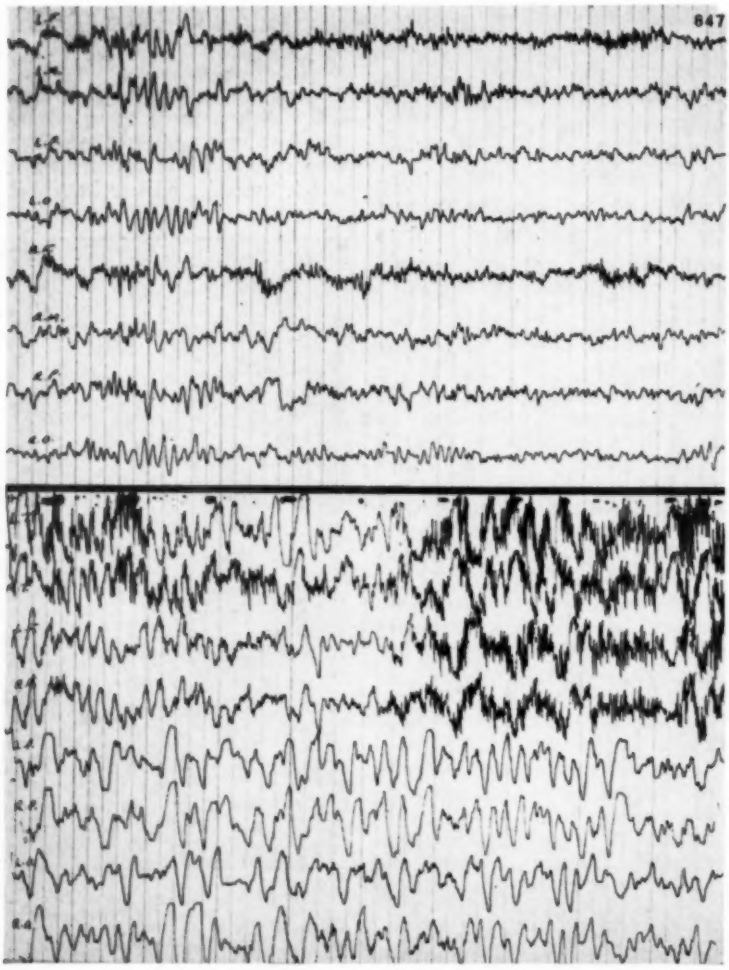

Fig. 2.—Electroencephalogram showing generalized instability. There is generalized slow activity one minute after hyperventilation.

Dysphagia, drooling, cyclic vomiting, and breath-holding had never been noted in the child. Emotional upsets had been quite marked for months and had often been manifested by stub-

for infectional arthritis. Both parents were of pure English descent, and close check revealed that no marriage with Jewish individuals had occurred. G. W. had one sister, aged

12 years, who suffered from nervousness and abdominal pain and was a behavior problem up to 3 years ago when improvement began.

The patient was of slender build, 52 inches tall, with a weight of 51 pounds. He appeared rather pale and his gait was awkward. Ability to move the fingers quickly was markedly reduced. There was evidence of a left convex dorsolumbar scoliosis with 1 inch elevation of the right hip. The lower extremities were of equal length when measured in the flat position. Toe and heel walking were performed clumsily. The peripheral reflexes were very hypoactive.

Barium study of the upper intestinal tract was negative, as were radiograms of the dorsolumbar spine and the chest. The red blood cells numbered 3.96 million and the white blood cells 5,900 per cubic millimeter of blood. The hemoglobin concentration was 12.2 grams per 100 c.c. of blood. The differential count was normal as was the urine. The electroencephalogram was reported as indicative of dysrhythmia, grade II, generalized. Dr. Bonsett's description read as follows: "The significant abnormality in the record consists of brief episodes of higher amplitude irregular discharges occurring simultaneously in all head regions. The activity is not synchronous. With hyperventilation, there was a very good buildup of slow activity. This persisted for an abnormal length of time following hyperventilation. The principal characteristic of the record is instability. The simultaneous discharge of slow activity in all head regions is suggestive of a deep seated midline disturbance." An electroencephalographic tracing was made on the 12-year-old sister, who was found to be normal.

The child was observed closely for any change in his reactions. The blood pressure taken in the lying position was found to be 102/65 mm. Hg. This figure was found to drop to 95/60 mm. Hg when the patient suddenly rose to standing position. The drop is slight, yet it is more significant since the usual expected elevation did not occur. Dizziness was not noted. It is reasonable to believe that the attack of syncope on rising from the bathtub was aggravated by sudden temperature change—warm water to cool atmosphere. The abdominal pain did not recur during hospitalization, yet anorexia was a persistent problem. The child was insensitive to heavy pretibial pressure and to pinprick. Corneal ulceration was not found.

Addenda:

Wechsler Intelligence Scale for Children:

Verbal I.Q. 109.
Perform. I.Q. 107.

Porteus Maze Mental Age:

8½ years.

COMMENT

A case of familial dysautonomia in a non-Jewish child is reported. The child showed all of the cardinal symptoms with the exception of disturbance in the swallowing reflex.

I express my appreciation to Dr. Francis P. Sheehan, M.D., for aid in gathering the data, and to Dr. Chas. A. Bonsett, M.D., for his electroencephalographic interpretations.

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LEPTOMENINGITIS DUE TO GAFFKYA TETRAGENA

Report of a Case Treated With Chloromycetin and a Brief Review of the Literature

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ALTHOUGH infections caused by *Gaffkya tetragena* are rare, leptomeningitis is even more rare. A perusal of both the American and foreign literature reveals only 15 cases of leptomeningitis attributed to *Gaffkya tetragena*. Bezançon and Lepage,[2] in 1898, reported the first case. The other 14 cases were reported by Griewe and associates[10] (1899), Oettinger and Malloizel[16] (1906), Pende[18] (1907), Vincent[23] (1908), Ramond and Rèsibois[21] (1915) 2 cases, Perfetti and Monziols[19] (1918), Lesehke[13] (1919), Blum and associates[3] (1923), Bonnano[4] (1931), Reiman[22] (1935), McGowan and Kisner[14] (1939), Criscitiello[6] (1939), and Leach and Medinger[12] (1941). From 1941 to 1957 no cases of *Gaffkya tetragena* leptomeningitis were reported. However, there were a few reports of endocarditis,[1, 5, 8, 11] gingivitis,[17] sinusitis,[7] and carbuncle[24] caused by this organism. The purpose of this paper is to report the sixteenth case of *Gaffkya tetragena* leptomeningitis, to make a brief review of the literature, and to outline and discuss briefly the characteristics of this illness.

From the Community General Hospital.

REPORT OF CASE

The patient, R. S., is a 12-year-old white boy who was admitted to the hospital by ambulance in a state of unconsiousness and repeated convulsions. The present illness started the day prior to admission with the symtoms of dizziness, vomiting, and fever. The vomiting became intermittent and projectile. The dizziness increased and changed gradually to drowsiness and then unconsciousness accompanied by convulsions. The past history is negative except that during infancy and childhood the patient has been considered "sickly."

Physical examination revealed a tall, underweight 12-year-old boy, unconscious, cyanotic, with twitching of all of the extremities. Pulse was 100; respirations 20. Neurological examination revealed nuchal rigidity and possible Kernig's sign. Ophthalmoscopic examination was noncontributory. Several spinal fluid studies were made, the first, on April 30, 1956, revealed clear fluid without pellicle; 23 cells per cubic millimeter, all lymphocytes; 1 plus Pandy reaction; 126 mg. per cent protein; and 310 mg. per cent glucose. The blood glucose was also elevated (350 mg. per cent), but within a day both the blood and spinal fluid glucose returned to normal and remained normal throughout the entire course of the illness. This transient hyperglycemia was attributed to the

convulsive state and is believed to be caused by increased intracranial pressure and increased secretion of epinephrine, a phenomenon analogous to the so-called "diabetic piqûre." A Gram stain of the spinal fluid revealed scattered extracellular gram-positive cocci which had a tendency toward

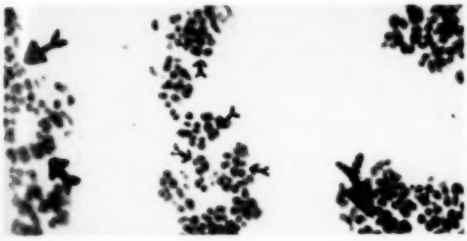

Fig. 1.—Gram stain of colonies from blood agar plate. Note characteristic tetrads. (×650.)

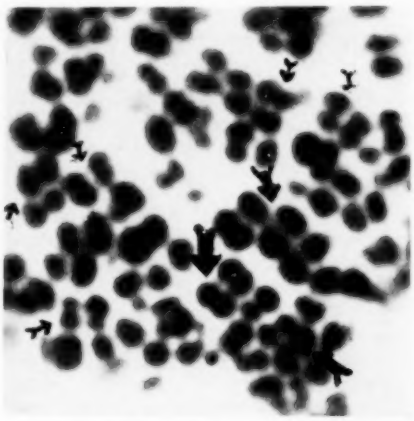

Fig. 2.—Gram stain of colonies from blood agar plate. Note again well-formed tetrads. (×2,000.)

tetrad arrangement, were seemingly encapsulated, and, in brief, resembled *Gaffkya tetragena*. The possibility of this organism being a primary or secondary invader was considered.

The spinal fluid study was repeated on May 2, 1956, with the following result: clear fluid without pellicle; 10 cells per cubic millimeter; all lymphocytes; 2 plus Pandy reaction; protein 90 per cent; sugar 41 per cent; colloidal gold curve 4433210000 (first zone or paretic curve). The possibility of cerebrospinal syphilis was excluded, however, by a negative Kahn reaction and the absence of a history of syphilis.

Both aerobic and anaerobic cultures were made on chocolate agar and brain heart infusion. The anaerobic culture yielded no growth after two weeks and was discarded. The chocolate agar also revealed no growth after two weeks. After 48 hours there was no visible growth in the brain heart infusion but on the fourth day growth was visible and characterized by a viscous sediment. Subculture was started on blood agar plate and after 24 hours a few small colonies appeared which could be well studied the following day. They were small, delicate, circular, convex, whitish-gray, slightly opaque, shiny and slimy. There was a slight green or alpha type hemolysis around the colonies. After a few days the colonies became whitish-gray and then whitish-yellow. Gram stain of the young colonies revealed pure culture of gram-positive cocci arranged generally in tetrads and diagnosed as *Gaffkya tetragena* (Figs. 1 and 2). The older colonies on direct smear revealed fewer tetrads. The organism coagulated milk, did not liquefy gelatin, and fermented carbohydrates (lactose, dextrose, and sucrose). It was found to be sensitive in vitro to Chloromycetin (10 meg.); erythromycin (5 meg.), and dihydrostreptomycin (10 meg.). It was not sensitive to Aureomycin (10 meg.), penicillin (5 units), Terramycin (10 meg.), and tetracycline (10 meg.).

Fig. 3 gives a comparative study of the medication used and its effect on the patient's fever during the 15 days of illness. The study of Fig. 3 and of the patient's hospital course gives a clear picture of the progress of the illness as influenced by antibiotic therapy. After 48 hours of Dihydrocillin therapy the patient failed to improve and became worse. His fever increased and he relapsed into coma after a short period of consciousness following admission. His convulsions

became more frequent and his cyanosis increased. The severity of the convulsions was an outstanding clinical feature, on two occasions requiring 3 ¾ grains sodium Amytal intravenously. After Chloromycetin therapy was started, the patient improved very quickly and within two days sat up in bed, conscious, and temporarily afebrile. This turn toward complete rehabilitation continued despite withdrawal of Dihydrocillin, and the patient hereafter remained asymptomatic except for intermittent low-grade fever. He was discharged completely recovered and still is in good health 21 months after his illness. Spinal fluid studies done prior to the patient's discharge from the hospital were all negative.

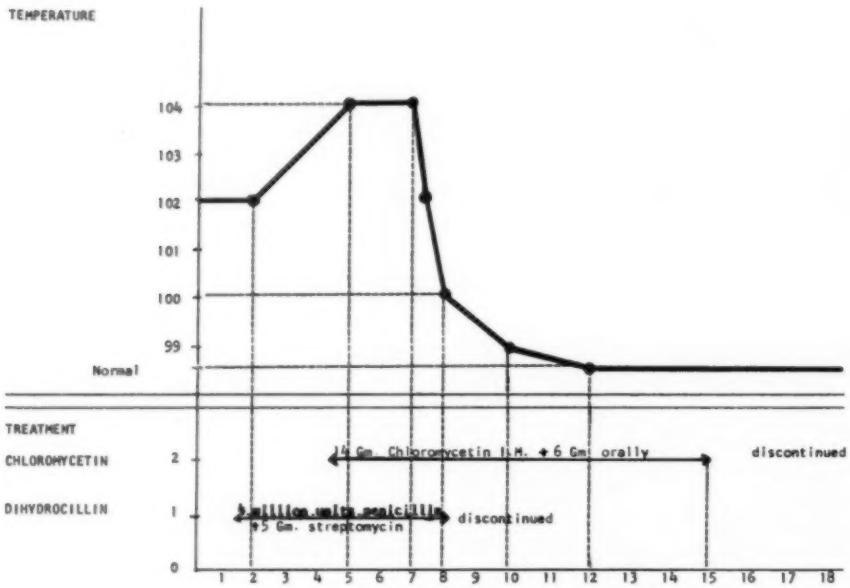

Fig. 3.—Correlation between fever and antibiotics therapy during the 15 days of illness.

REVIEW OF THE LITERATURE AND DISCUSSION

Gaffkya tetragena, as the name indicates, was first described by Gaffky[9] in 1881. The characteristic features of the organism are fairly well known. That the organism may cause leptomeningitis is less well known. We believe that the case presented here possesses the necessary clinical and bacteriological characteristics of *Gaffkya tetragena* leptomeningitis. The diagnosis depends in final analysis on the typical tetrad arrangement of the coccoid organisms, their cultural characteristics and microbic dissociation. The 15 previously reported cases have already been enumerated and their individual features outlined.

The general characteristics of the illness are tabulated in Table I, which points out that *Gaffkya tetragena* leptomeningitis is a very rare but, up to now, a very serious infection, with more than 75 per cent fatality. It is quite certain, however, that with the advent of antibiotics the outcome will be brighter. This will depend on vigorous antibiotic treatment, the drug

TABLE I. CLINICAL CHARACTERISTICS OF *Gaffkya Tetragena* LEPTOMENINGITIS

INCIDENCE	AGE	SEX	ONSET & TYPE	DURATION	OUTCOME	TREATMENT	SEQUELAE
Extremely rare (only 16 cases published)	Strikes adults (younger patient, 12 years old; older patient, 58 years old)	Favors male over female by a ratio of about three to one	Onset sudden; inflammation may be suppurative or nonsuppurative	Short, 1-5 weeks; occasionally longer	About 75 per cent fatalities (up to now, 7 deaths and 9 recoveries)	No standard treatment; antibiotics best; preferably Chloromycetin or Terramycin	Generally none

of choice being the one so proved by in vitro sensitivity study and in vivo therapeutic trials. In the absence of sensitivity study, Chloromycetin and Terramycin are considered best. It is very probable that *Gaffkya tetragena* leptomeningitis is not as rare as it seems to be. Awareness of its occurrence will help in detecting its existence.

SUMMARY

This paper deals with the clinical and bacteriological study and the successful antibiotic therapy of a 12-year-old boy with leptomeningitis due to *Gaffkya tetragena*. Only 15 other cases of leptomeningitis caused by this organism have been reported, with 75 per cent of them fatal. The infection is probably more common than the number of reported cases suggests. The prognosis should be much better in the era of vigorous antibiotic therapy.

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Manners and Success

There have always been various opinions relative to the influence of personal manners upon the professional success of physicians; and doubtless there still are. Notwithstanding, the majority of individuals, in and out of the profession, incline to yield the palm to that unaffected and dignified courtesy which is ever the prompting of a kind heart and a sensible head. The simple graces of manner which a hearty interest in human welfare always spontaneously prompts, are never more acceptable than when manifested in the sick-room, or towards the sufferer from unforseen casualty. The usages of true politeness are ever the most politic—to look at them in no higher light. Every noble and tender sentiment, however, prompts the medical practitioner to observe not only the outward, but the inward amenities of life. We therefore regret, when we observe, as we sometimes do, an aspirant for fame and success in our calling, inclined to adopt a strained, eccentric and unnatural manner—or worse than that, a blunt, rude, pert or overbearing deportment towards his elders if not his betters. There sometimes are birds, barely fledged, who endeavor very absurdly to plume as broad a wing as older and higher fliers. They are exceedingly apt to be "taken down a peg," after a time. It is not, however, this harmless little arrogance, which experience soon cures, that most needs animadversion. It is the insolent, unmannerly tone and words of juniors to seniors, which unfortunately has come to late to characterize "Young America," in every sphere of life and in all sorts of occupations.

FROM THE BOSTON MEDICAL AND SURGICAL JOURNAL, AUG. 19, 1858.

A CASE OF MALIGNANT SACROCOCCYGEAL TERATOMA

E. M. McConnell, M.D.
Liverpool, England

INTRODUCTION

THE development of malignancy in a sacrococcygeal tumor is uncommon. The first example was recorded by Rudolphy.[9] Lisco,[6] in an extensive survey of the literature, found seven definite examples of this condition, and added two cases from his own records. Ravitch and Smith,[7] in a review of 48 published cases of congenital sacrococcygeal tumors, found evidence of malignant change in 8 cases (17 per cent). A similar incidence of malignancy occurred in the series described by Gross, Clatworthy, and Meeker[3]—7 instances of clinical and histological malignancy out of 40 cases. Hickey and Layton[4] described one example of clinical and histological malignancy in a series of 9 cases. In all of the cases described, only one element of the teratoma assumed a malignant character, and the commonest type of tumor resulting was a papillary adenocarcinoma.

In view of the comparative rarity of the condition, it was felt worth recording the following single case in which symptoms due to malignant erosion of the lumbar vertebrae were the first indication that an apparently benign teratoma, removed within 24 hours of birth, had undergone a malignant change.

From the Department of Pathology, Liverpool Radium Institute.

CLINICAL HISTORY

A female child was noted at birth to have a large (12 by 6 cm.) sacrococcygeal tumor involving the lower half of the sacrum and the coccyx and displacing the anus forward. This was successfully removed within 24 hours of birth, and histological examination of the tumor showed a typical benign teratoma, which included squamous and glandular epithelium, nervous tissue, muscle, cartilage, fibrous and vascular tissue. All these various elements were well differentiated and adult in type and there was no suggestion of malignancy. The child remained completely well for 2 years and 9 months, when she complained of pain in her back following a fall. Clinical examination at this stage showed a fretful but otherwise healthy and well-nourished child; however, there was tenderness over the lower lumbar spine and a recurrent swelling was noted in the buttocks. Rectal examination revealed a firm tumor lying between the rectum and sacrum, and radiological examination showed metastatic deposits in the third and fourth lumbar vertebrae with complete collapse of the third lumbar vertebra. A biopsy examination of the gluteal tumor showed a papillary adenocarcinoma.

Radiotherapy to the gluteal tumor and the vertebral column caused a regression in the size of the tumor and relief from pain. However, the child's condition deteriorated rapidly; she was pyrexial, and radiological examination of the chest showed enlargement of the hilar lymph nodes and infiltration of both lung fields. In view of the presence of the malignant sacrococcygeal

tumor and metastatic deposits in the vertebral column, the pulmonary changes were presumed to be neoplastic in nature. Death occurred five months after the initial complaint of pain in the back.

PATHOLOGY

Autopsy showed an extremely emaciated female child, with a protuberant abdomen, edema of the legs, and scattered petechial hemorrhages on the body surface. The biopsy incision was well healed and there was no external evidence of any gluteal tumor. Internally, a large, friable tumor was present in the pelvis. It was lying posteriorly to the rectum, invading the sacrum and coccyx, spreading anterolaterally around the pelvis and superiorly into the psoas muscles from where it had invaded the second and third lumbar, and the sixth and seventh thoracic vertebrae; complete collapse of the third lumbar vertebra had occurred.

The liver was enlarged to twice normal size due to multiple deposits of tumor. These deposits varied in size between 1 and 20 mm. in diameter and appeared to be of two types. The larger tumors were soft in consistency, with necrotic and hemorrhagic changes, and appeared to be metastatic deposits from a malignant tumor. The appearance of the smaller nodules was very suggestive of miliary tubercles; similar small nodules were scattered throughout the spleen.

Within the thoracic cavity there was a small straw-colored pleural effusion on the right side. The hilar lymph nodes were enlarged up to 1.0 cm. in diameter, their cut surfaces presenting areas of both caseation and hemorrhage. Metastatic deposits of tumor were scattered throughout both lungs. They presented a similar appearance to the larger hepatic tumors, being very soft in consistency and white in color, with areas of necrosis and hemorrhage. The right lung, in addition, was diffusely infiltrated by nodules, 1 to 2 mm. in diameter, which were again very suggestive of miliary tubercles. The other organs showed no significant abnormality.

Histological examination of the sacrococcygeal tumor showed a papillary adenocarcinoma similar to the biopsy, with a very characteristic appearance (Fig. 1). The papillae comprising the tumor were formed of an extremely delicate, vascularized branching network of connective tissue, covered by a single layer of epithelium-like cells, which had a large, spherical nucleus, poor in chromatin and pale staining (Fig. 2). Some of the cells were multinucleate, and in a few cases a nucleolus was present. The cytoplasm was scanty and somewhat granular. A striking resemblance to a string of beads was given by this single layer of cells with almost naked nuclei arranged over the connective tissue papillary proliferations. In some areas the cells were arranged in sheets; here the cytoplasm tended to be more abundant and foamy (Fig. 3). In other areas the papillary structure gave way to an acinar arrangement, the cells having flattened nuclei and scanty cytoplasm. This latter picture appeared to be the result of a degenerative change in the delicate connective tissue in the core of the papillae, and was associated with areas of a myxomatous type of degeneration and of necrosis.

Deposits of a similar tumor were present in the liver, lungs, hilar lymph nodes, and in various vertebrae (Fig. 4).

The small nodules noted macroscopically in the liver, spleen, and right lung were confirmed histologically as being miliary tubercles. The hilar lymph nodes showed a caseous tuberculosis in addition to the metastatic tumor. Histological examination of the lungs also showed a tuberculous bronchopneumonia. These bronchopneumonic foci were misdiagnosed at the autopsy as areas of tumor. Tubercle bacilli were demonstrated in the caseous hilar lymph nodes, liver, lungs, and spleen.

Fig. 1.

Fig. 2.

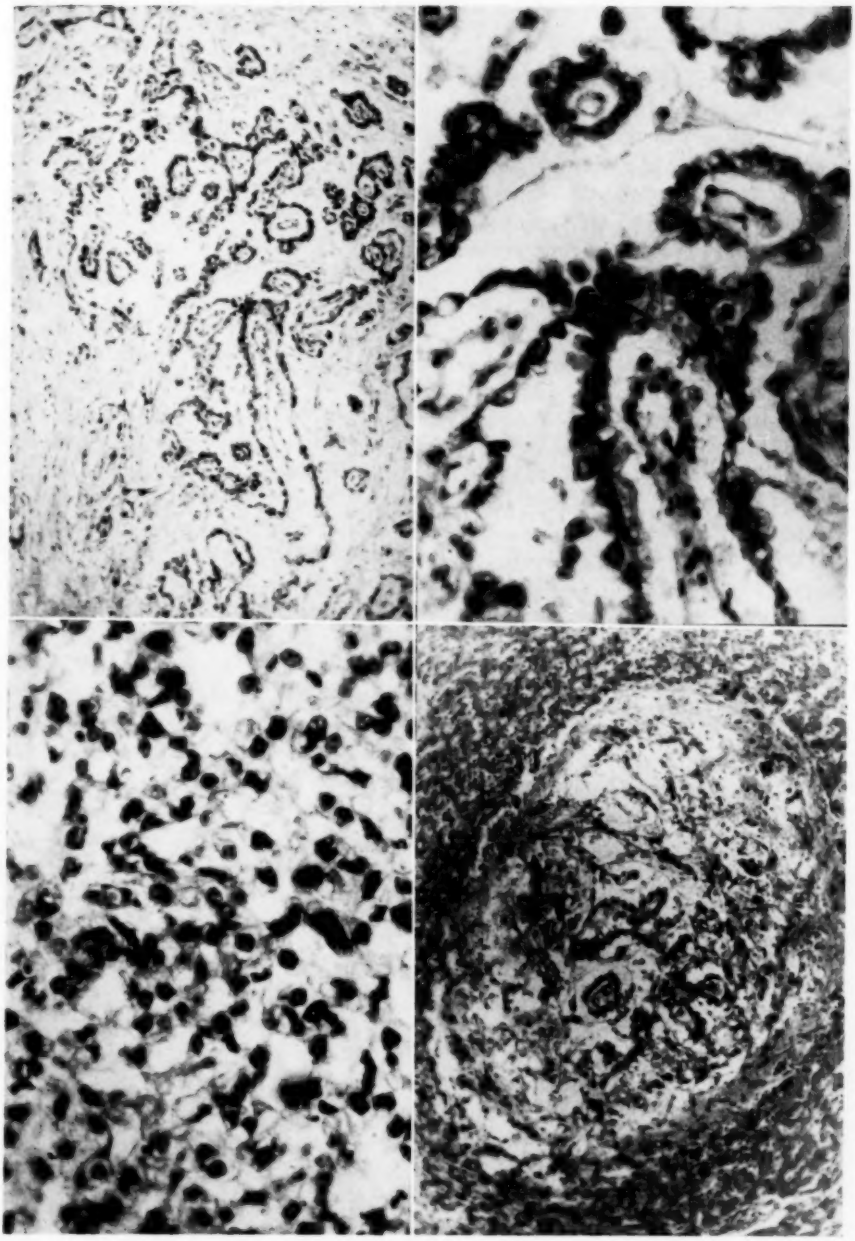

Fig. 3.

Fig. 4.

Fig. 1.—Typical papillary appearance of the tumor (×100).
Fig. 2.—Higher magnification showing detailed structure of the papillae (×400).
Fig. 3.—Sheetlike arrangement of cells (×400).
Fig. 4.—Secondary deposit of the tumor in the liver (×100).

DISCUSSION

The problems of etiology and nature of sacrococcygeal teratomas have aroused interest for many years; however, their latent malignancy has not always been appreciated. Law[5] advocated removal of pelvic tumors having sacral attachments owing to their tendency of malignant degeneration. Stewart, Alter, and Craig,[10] Lisco,[6] Gross and associates,[3] and Hickey and Layton[4] have all stressed the need for adequate removal of sacrococcygeal tumors in the neonatal period, possibly followed by prophylactic radiotherapy, as a malignant change is usually sited at the base of the tumor, involving the sacrum and coccyx. Gross and associates and Hickey and Layton consider that risk of subsequent malignant degeneration following adequate surgical removal in the neonatal period is small. In the series of 30 cases treated in the neonatal period by Gross, malignancy supervened on 2 occasions; Hickey and Layton, in a review of 38 cases treated prior to 4 months of age, found only 2 examples of subsequent biological malignancy. The prognosis is far less favorable when adequate removal is not undertaken within this period, and the majority of cases recorded in which a malignant change has occurred fall into this category. Hickey and Layton, in a review of 25 cases in which therapy was delayed until after 4 months of age, found evidence of subsequent biological malignancy in 16 cases.

In the present case an extensive resection of an apparently benign teratoma was successfully performed within 24 hours of birth, the manifestations of the malignant transformation in residual tumor tissue being delayed until after a symptom-free latent period of 33 months, which is considerably longer than the average in the cases recorded. Symptoms referable to a distant metastasis drew attention to the malignant change, the child complaining of pain and tenderness in her back, which was initially attributed to trauma but was, in fact, the result of malignant infiltration and collapse of a lumbar vertebra.

When a malignant change occurs in a teratoma, it usually involves one tissue element only, and the sacrococcygeal teratomas are no exception to this rule. There are eleven cases recorded in the literature in which the histological features of the tumor are described, and although in some cases the descriptions are brief, it is very interesting to note that in nine of these cases—Rudolphy,[9] Fletcher and Waring,[2] Bergmann,[1] Stewart and associates,[10] Renner and Goodsitt,[8] Lisco,[6] Ravitch and Smith,[7] and Hickey and Layton,[4] the malignant tumors were papillary adenocarcinomas with the same characteristic appearances as the present case. The prognosis in all these cases is very bad, death occurring within a few months of the diagnosis of malignancy, with local recurrence and metastasis to the liver, lungs, and lymph nodes.

The clinical picture in the present case was complicated terminally by a generalized tuberculous infection, which accounted at least in part for the rapid deterioration in the child's condition, and for the pyrexia, attributed during life to the neoplastic condition.

SUMMARY

A case of malignant degeneration in a sacrococcygeal tumor removed

within 24 hours of birth is described. After a symptom-free latent period of 2 years and 9 months, pain in the back, due to malignant infiltration of the lumbar vertebrae, drew attention to the malignant transformation. The resultant tumor was a papillary adenocarcinoma. The clinical and autopsy findings were confused by a generalized tubercuIous infection.

I wish to thank Dr. M. S. Milln for permission to publish the clinical details of this case.

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Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, M.D., EDITOR
JOHN M. CRAIG, M.D., ASSISTANT EDITOR

CASE 1.—This 8½-year-old white boy entered The Children's Medical Center with the chief complaint of a painless lump on the right side of the neck of fourteen months' duration.

At age 4 months, he was given 250 roentgens of x-ray therapy to an hemangioma of the anterior chest wall, and 300 roentgens to a similar lesion of the left arm. One year later, a second treatment of 300 roentgens was given to the chest wall lesion; both hemangiomata subsequently underwent complete regression.

At 7 3/12 years of age, a removal of the tonsils and adenoids was performed elsewhere because of repeated colds. Immediately postoperatively, he complained of earache bilaterally but had no evidence of discharge or cervical adenitis. Two weeks after that operation, his mother noted a firm nontender lump on the right side of the neck which persisted, with little increase in size, until the present admission. It had remained painless and had never interfered with swallowing or breathing.

The physical examination at the time of admission revealed normal vital signs in a well-developed, moderately obese boy who did not appear ill. There were nearly a dozen firm, nontender, irregular masses palpable throughout the right side of the neck. Other smaller, discrete nodes were palpable on both sides of the neck in the anterior cervical chains and base of the neck posteriorly. In the midline, just inferior to the thyroid cartilage, was a 0.5 cm. palpable nodule, interpreted as a "Delphian node." The thyroid gland was not palpable. The remainder of the physical examination was not remarkable.

The laboratory examinations of the blood and urine disclosed no abnormal values. Roentgenograms of the chest and long bones revealed no abnormalities. Administered radioactive iodine revealed a 40 per cent uptake over the thyroid gland area and none over the cervical lymph nodes.

On the second hospital day, an operation was performed.

CASE 2.—This 15-year-old white girl, with a chief complaint of swelling in the neck of three and a half years' duration, was seen in The Children's Medical Center Outpatient Department because of a mild discomfort of the anterior neck, radiating to the ear.

The thyroid gland was then slightly tender and symmetrically enlarged (although one observer felt that the left lobe was larger). A diagnosis of adolescent goiter was made and she was given thyroid extract, 60.0 mg., then 90.0 mg., daily, for a period of two years. At the end of this time, the protein bound iodine was 3.6 mg. per cent and the radioactive iodine uptake, 49 per cent. Scanning revealed a nonfunctioning left lobe with an irregular distribution of radioactivity in the right lobe. The patient was not seen again over the next year and a half. Over the entire three and a half years her menstrual periods had been irregular.

At the time of admission, physical examination revealed normal vital signs and a well-developed and nourished girl who did not appear ill. No findings suggestive of abnormal thyroid function were present. The thyroid gland was bilaterally, but slightly, enlarged. The right lobe was smooth and normal in consistency. The left lobe was firm, with slight nodularity and with a single definite nodule at the lower pole. The tonsillar nodes were palpable but there was no other cervical gland enlargement. No "Delphian node" was present.

Laboratory examinations of blood and urine were unrevealing. The radioactive iodine uptake was 45 per cent and a scan revealed symmetrical radioactivity over both lobes.

An operation was performed on the third hospital day.

DISCUSSION

DR. OLIVER E. COPE.*—Well, I suspect this first case offers no dispute. The preoperative diagnosis must have been a papillary carcinoma of the thyroid. The only other lesion that gives palpable lymph node enlargement in the neck is thyroiditis and I think that thyroiditis should have given a thyroid gland which was palpable. The distribution of the lymph nodes, their description, and the absence of significant thyroid enlargement, spell papillary adenocarcinoma arising in the thyroid with a thyroid lesion that is too small to be identified. Now, that is not an uncommon experience. The background of this child is of interest, of course, because of the radiation for hemangiomata in the early months of life. We are all aware now that such irradiation is incriminated as an etiologic stimulus for the growth of malignancy in the thyroid gland, in age groups from 4 to 15 years. Duffy and Fitzgerald,[1] at the Memorial Hospital in New York, reviewing their 28 cases of carcinoma of the thyroid in childhood, observed that 9 children had had thymic irradiation; they hesitated to lay any significance on this in their paper of 1950. Simpson and Hempelmann[2] and two groups in Chicago, Clark[3] and Slaughter,[4] looked up their statistics and found a significant relationship between the incidence of carcinoma and previous irradiation of the thymus. For example, the entire 15 cases Dwight Clark had seen between the ages of 4 and 15 had had previous irradiation of the thymus. The other incidences weren't quite so high. My own experience is very limited and isn't statistically significant. The obvious reason for this is that, at our hospital, Dr. George Holmes, long ago, believed that "thymic enlargement" was probably a physiologic state and refused to radiate

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thymuses—yet at that time a good many of the hospitals in Boston and the country over were taking thymic plates and exposing children to radiation if the thymuses were enlarged. The only differential that should be considered is thyroiditis; the description as given is not compatible with thyroiditis for, if these lymph nodes in the right thyroid region are significantly large, with the "Delphian lymph node" enlarged, even though there is nothing palpable and no primary lesion palpable in the gland, I would still be forced to make a preoperative diagnosis in this child of carcinoma of the thyroid.

Now, the second case is more problematic because you have a variety of diagnoses that are plausible, and because the physical examination as described doesn't give one the chance to refine the diagnosis beyond the statistical evaluation of the possibilities. These exercises are not really like medical or surgical professional consultations because you hope that the consultant will see something or observe something that you have missed. That is true in the physical examination, in the history, in observations of clinical behavior, and in the x-ray examination. The value of the physical examination is the detailed appreciation of the observer.

The thyroid in the second case was found to be slightly tender and symmetrically enlarged, although one observer thought the left lobe was more prominent. The presence of tenderness ordinarily indicates inflammation, and in the thyroid that can be due to a hemorrhage as well as to other types of inflammation. Tenderness is not altogether a reliable sign for the exclusion of carcinoma. Very recently, one of our young student nurses with a lump in the thyroid, complained of tenderness and I excluded carcinoma on this basis; she turned out, a year later, to have a papillary carcinoma. The fact that one observer felt the left lobe was more prominent is extremely important because, unless the child had dextrocardia, the prominence of the left lobe indicates a process in that lobe which is not present in the right. Since the right lobe of the thyroid is usually, on the average, 25 per cent heavier than the left, the largest tissue mass ordinarily is to be felt in the right lobe.

Scanning for radioactive iodine uptake revealed a nonfunctioning left lobe with radioactivity in the right lobe in an irregular distribution. Now, here again, there is an indication that there is some process in the left lobe which has less than normal function in spite of its greater size. This is an indication, presumably since it is localized, that it is probably neoplastic process.

DR. JOHN CRIGLER.—Dr. Cope, I think that a note should be made in respect to the original scan. I think that you should not put much emphasis on the report as given here; the amount of activity in the gland was not adequate for a satisfactory scan at that time. I think you really can't judge whether there was any localization of radioactivity in that gland.

DR. COPE.—I am glad that you point that out because I was going to use the difference between that and the subsequent scanning, which shows an even distribution.

It is said that this thyroid gland was enlarged bilaterally; this means that the initial process presumably had been a diffuse bilateral one, and that there has been a localization in the left lobe, not found in the right, which indicates an additive process. Here is where I found my role difficult because the left lobe was firm and presented a definite nodule in the lower pole, with a suggestion of small nodularity throughout. When one palpable adenomatous nodule is present, it is very frequently found that multiple satellite nodules are also present in the thyroid. Another interpretation of these findings may be that a malignant nodule is present and it is spreading, because this could be a description of an invasive thyroid carcinoma.

I will assume that she had an adolescent goiter. I think that possibly the tenderness was due to a hemorrhage, and that hemorrhage induced a secondary inflammation.

A word about scanning. If you have a nodule covered by a good-sized rim of functioning tissue, I think you will agree that it is very hard to tell if that is a "cold nodule," or a "functioning nodule"—so counting doesn't always tell us if we are dealing with a "cold" or a "non-functioning" nodule, or whether it is a functioning one. It makes some difference in the statistical appraisal because the less the function, the less the differentiation of cells and the greater the likelihood of malignancy. Let us run briefly through the possibilities. This is not the ordinary thyroiditis, that I can see. Second, it is not a neoplasm because it has been a localized disease for too long without lymph node metastasis. Third, the process started as a diffuse one, and therefore it is a lesion which has developed on a previous diffuse adolescent goiter or hyperplastic process. On such a basis the lesion may be a number of different things. It can be a well-differentiated adenoma, or less well differentiated, as a fetal type of thyroid tissue. It may be a benign papillary cystadenoma. It has been there for quite a little time, and I wonder why, if it is a papillary carcinoma, there aren't lymph nodes.

In summary, my preoperative diagnosis would be that this is a diffuse adolescent goiter with an adenoma in the left lobe. There is a 50 per cent chance, at this age, that this is a malignant adenoma. If I were operating, I would really be operating to determine the diagnosis but, since you are requiring me to make a diagnosis, I will say a benign follicular adenoma. On the basis of the moderately active function study, I would consider a follicular type of adenoma. That is a pure guess, really based on statistics.

DR. CRAIG.—May we have the preoperative diagnosis of the Surgical Service?

DR. L. MARTIN.—The preoperative diagnosis on the first case was thyroid carcinoma and, in the second case, we thought that this was probably a benign disease but we couldn't be certain.

DR. CRIGLER.—I was interested in Dr. Cope's statement to the effect that he likes to feel these glands himself, because as I read over the protocol on the second case, my description of it would be entirely different. I thought that the left lobe felt rather fibrous,

granular and lobulated, but not nodular. It was as if we were dealing with a scarred gland.

DR. CRAIG.—Were there any studies of her thyroid function?

DR. CRIGLER.—Yes, clinically she was euthyroid, but you can, of course, miss what is called a compensated hypothyroid state.

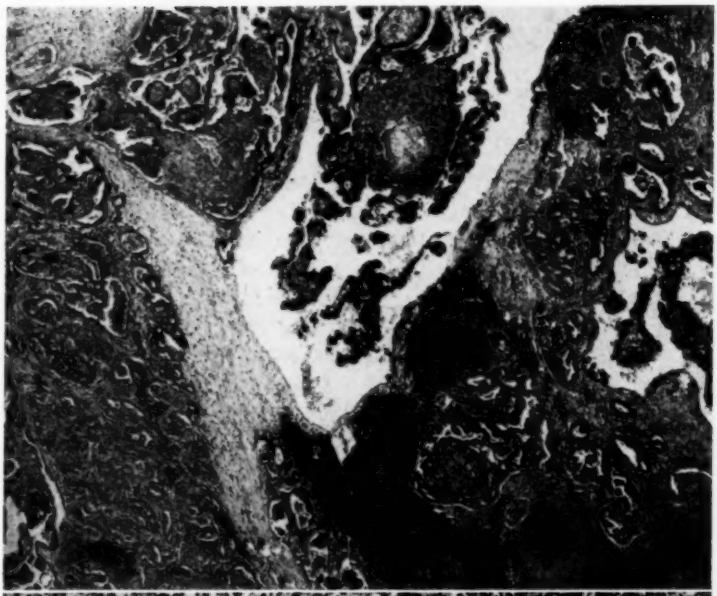
DR. CRAIG.—The first child, as was suspected by all concerned, had a papillary adenocarcinoma of the thyroid. Both lobes and the lymph nodes on both sides of the neck were involved. There was evidence of vascular invasion, as well as quite marked lymph node invasion. This tumor was comparatively mature in that the cells were quite uniform, quite regular, and there were not too many mitotic figures (Fig. 1).

The second case, we thought, was a fairly specific example of Hashimoto's thyroiditis or struma lymphomatosa. There was a tremendous amount of lymphoid tissue in many areas, some forming even secondary lymphoid follicles. Colloid was present, but the acini were quite broken up and occasionally there were individual acinar cells which were diffusely distributed—which may, I suppose, be part of the hyperplastic state of this process. In some areas, definite eosinophilic degeneration of the acinar epithelium could be found, which is supposedly a sine qua non for the diagnosis of this type of "thyroiditis" (Fig. 2).

DR. ROBERT E. GROSS.—I would like to ask Dr. Cope his feelings about therapy of carcinoma of the thyroid. The number of cases that we have seen comprises a very small group. In general, we have done a subtotal thyroidectomy. We have usually removed the involved side entirely and gone well over to the other side, leaving a little shell posteriorly to be sure to protect the recurrent nerves and the parathyroid gland, generally leaving enough thyroid tissue to carry the patient along in an euthyroid state, but not worrying too much if we do not. At the same time an extensive removal of the nodes and involved tissues of the neck is carried out. We have not uniformly used a radical block removal of tissues, and we have not taken the internal jugular vein or any of the muscles routinely, but have taken only those structures which seemed to be involved by the tumor. We have not routinely used x-ray or radioactive iodine therapy, rather holding these in reserve if there should be recurrence. I am very much impressed with the slowness of the growth of most of these which we have seen. Just a few weeks ago we had a child, 7 years of age, with a known mass in the neck for three years, which I am sure had been a malignant process from the start. On the whole, as we see these in youngsters, they are very slowly growing tumors and can be fairly conservatively managed.

DR. COPE.—I agree completely with you. To my mind there is no other tumor like this in any other organ of the body. Papillary carcinoma, unless it is a part of a mixed tumor of the thyroid, is in real terms a curable disease, and it is no more malignant in children that you just quoted than in the patient in the teens or the second and third decade, or any decade in life. Although it is usually a slowly

Fig. 1.



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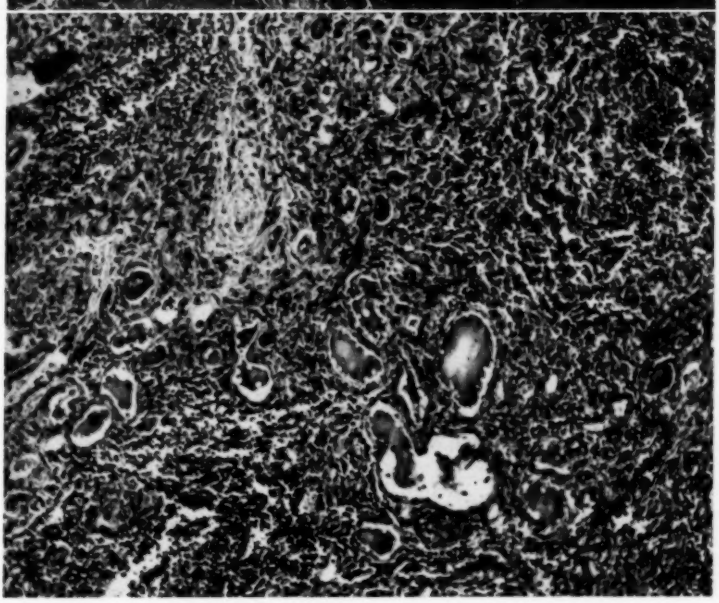

Fig. 1.—Case 1. Lymph node. Metastatic thyroid carcinoma is involving the local lymph node. (Toluidine blue – eosin; ×45.)

Fig. 2.—Case 2. Thyroid. Marked lymphoid infiltration of the thyroid is present. A few colloid masses remain in acini and in the lymphoid stroma. (Toluidine blue – eosin: ×150.)

growing tumor, variations in growth rate occur, yet it has to be called malignant because if you leave it alone, and don't do anything about it, it will throttle the patient. It has an extraordinary predilection for growth in the lymph nodes and it flourishes in the lymph nodes with greater abundance of growth than in the thyroid itself. How big was the primary lesion?

DR. CRAIG.—Not more than 1.0 cm. in diameter.

DR. COPE.—If the tumor is a pure papillary growth and not mixed, it stays in the lymph nodes for years and only slowly invades structures. Until that happens, I agree with you that a conservative operation is the proper choice.

DR. CRAIG.—Dr. Cope, there are recent reports from the Cleveland Clinic concerning the use of suppressive doses of thyroid in the treatment of thyroid cancers.[5] Do you regard these tumors as hormonally dependent?

DR. COPE.—We have had the opportunity to treat 4 patients with this disease on so-called suppressive doses of thyroid gland. The student nurse that I described was on 3 grains of thyroid for a year, or a little more. It didn't do anything to the localized mass. The rest of her thyroid became atrophic. She had no lymph node involvement but still the primary lump was a good grape size. Perhaps, without the thyroid medication in that year and a half, it would have spread into the lymph nodes. We had another patient, a 22-year-old girl, with a left-sided lesion with bilateral lymph node involvement. I did the left side first, taking out the primary tumor. Unfortunately, she developed a severe staphylococcal operative infection. We put her on thyroid medication and allowed the infection to clear up before tackling the other side. In the initial months of thyroid therapy the remaining nodes on the opposite side became a little smaller; they reached a base level at eight months, and then began to increase in size—and this, in spite of 200 to 260 mg. of thyroid. I then operated on her again.

Let us not confuse the issue. You don't give thyroid therapy to suppress the growth of a papillary metastasis, but you give thyroid to a patient in whom you have removed nine tenths of the thyroid since you don't want to expose that remnant, small as it is, to undue pituitary stimulation.

DR. CRAIG.—Perhaps it is well to point out now that only about 50 per cent of thyroid carcinoma in children is papillary. The rest seem to be follicular in type. Bone metastases most frequently follow follicular types and I presume that it is true of lung metastases. Dr. Theodore Winship of Washington, who is very interested in this problem, has been able to collect some 45 cases of childhood thyroid cancer with follow-ups for ten years; 17 of these were still living with this disease after the first operation, and only 5 of the 45 were dead[6]—so that it is really quite a relatively nonfatal disease, as far as that goes.

The true nature of thyroiditis and its classification is still unsettled among pathologists and clinicians. There is almost no meeting of the minds between one author and another.

One of the largest series of cases reported by Lindsay to the Goitre Association in 1952[7] lists 170 cases of

struma lymphomatosum, 25 cases of giant cell and Riedel struma. Dr. William Meissner[8] places a majority of his cases in the nonspecific group, and much smaller numbers in the Hashimoto or struma lymphomatosum. Crile,[9] on the other hand, has a fairly even distribution of the thyroiditis cases between Hashimoto's, subacute, and Riedel's. Hendrick[10] includes, in his classification, a large number of cases of "acute thyroiditis." Some of these cases followed shortly after an upper respiratory disease and were not biopsied. All I wanted to do was to bring out the variation in labeling that has occurred in this field, which suggests a real lack of knowledge as to the true nature of the processes involved.

DR. COPE.—Dr. Crigler has given us an indication of what the left lobe was like, but what was the right lobe like at the time of operation?

DR. MARTIN.—The lymph nodes did not seem to be involved at all at surgery. The thyroid gland, on the operative table, looked quite different from what it seemed clinically. Both thyroid lobes looked just about the same at the operative table—diffusely granular, finely nodular and irregular throughout, and firmer than normal. The left lobe was more prominent than the right and a little firmer too.

DR. COPE.—Well, I now believe that the patient had typical thyroiditis because it is seen to be established as a diffuse thyroid disease. One of the questions always raised is—does it ever occur as a localized disease in one lobe? Dr. Craig, have you ever seen localized thyroiditis of the lymphoid type?

DR. CRAIG.—I don't believe so.

DR. COPE.—I thought I saw one patient once with a Hashimoto's type of thyroiditis involving predominantly one lobe, and there was very little to be seen in the other one. But you know, the more I see of the disease, I wonder how good my memory is because I never found one again. The other thing is that the lymph nodes are usually enlarged, in my experience, to some extent, but there is nothing characteristic about their microscopic appearance.

DR. CRAIG.—One thing that interests me about this patient is the problem of therapy. Many people believe that since this is a diffuse disease of the thyroid, and since patients can develop respiratory difficulties with compression of the trachea, a total thyroidectomy is indicated, rather than a subtotal thyroidectomy since a higher proportion of patients become hypothyroid anyway. Some people advocate total thyroidectomy when the patient first presents himself, to prevent respiratory obstruction, and to save the patient any further difficulty. Other people suggest radiation therapy, but probably that would be banned, though a recent article in one of the surgical journals even now recommends it in such cases.

DR. COPE.—I think almost everything has been suggested for this condition with suggestions of success, and yet ultimate failure—thiouracil, cortisone, and radiation. A purely mechanical (surgical) approach seems to work in the patients with obstructive symptoms, but the disease ultimately runs its course. In running its course, the disease may destroy a significant

amount of the secreting thyroid tissue so that the patients become hypothyroid. I have not been impressed with the practice of giving thyroid to relieve the thyrotropic stimulus on those poor little remnants and islets which you showed in your slides and do not feel that it does anything toward stopping the disease process per se. You operated on this patient to make a diagnosis, and that was common sense because you did not know what you were dealing with, and you were perhaps running a danger not to know. Now, having made a diagnosis at operation, you are there and what do you do? Some of the patients go on to the obstruction that Dr. Craig described, so I think that it makes sense to remove the anterior portions of the thyroid and then, once you have done that, you don't have to go back to do an operation for respiratory obstruction at a later time. If the patient subsequently develops hypothyroidism, logically you treat that situation but still you are treating the primary disease, really.

DR. GROSS.—Is this a common problem in the 15-year-old age group?

DR. CRAIG.—Not as we have seen it here, Dr. Gross. In the literature an appreciable number have thyroiditis starting at ages from 10 to 20; in a very small proportion, signs may date back to the first years of life. These numbers are very small, compared to the numbers seen at ages 40 to 50, where it is more frequently seen.

DR. COPE.—We had a rush of them in children that Nathan Talbot wrote up.[11] As I recall it, there were 15 or 16 cases in patients 10 to 15 years of age, all in a period of about five years. The last one was about five or six years ago. I haven't seen one since.

DR. CRAIG.—This is predominantly a disease of females in active menstrual life. In some cases there is good evidence that it is a disease of "autoimmunization."[12] In most pediatric textbooks it is not mentioned at all.

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Comments on Current Literature

MAMMALIAN VIRUSES AND RICKETTSIAE: NEW METHODS OF PURIFICATION AND RECOVERY

THE remarkable success of chromatography in the separation of amino acids, lipids, sugars, and many other substances has been an important factor in some of the recent advances in the field of biochemistry. The separation of proteins by these methods proved somewhat more difficult, chiefly because the large size of the protein molecule prevents its penetration into the adsorbent particle and limits the adsorption sites to those on the exterior. Thus, in the case of proteins, large surface is necessary for the attainment of reasonably high adsorption capacity. For a number of years inorganic gels, such as calcium phosphate, had been used with a considerable degree of success in the chromatography of typical proteins. Subsequently, however, new stable adsorbents derived from cellulose were employed, which, in addition to the necessary basic chemical and physical characteristics, have a large capacity for the adsorption of proteins. Peterson, Sober, and their associates[1] have described the preparation of such cellulose ion-exchange resins, DEAE-SF and ECTEOLA-SF, and their use in the column chromatography of proteins. The letter identification of these cellulose ion exchangers is taken from the reactants, since the structure of the attached groups cannot be specified exactly. One of these, ECTEOLA-SF, proved to be less promising in protein adsorption capacity, but was shown by a number of investigators to be of exceptional merit in the chromatography of nucleic acids. Since cellulose ion-exchange resins permit the chromatography of nucleic acids from various sources, it was suggested that these resins might be of use in the purification of nucleoproteins such as those of viruses and bacteriophages. Fractionation of the tobacco mosaic virus by this means was reported as early as 1956 by Commoner and his colleagues[2]: chromatography with ECTEOLA-SF not only of the natural tobacco mosaic virus but also of reconstituted virus nucleoprotein. Recently Taussig and Creaser[3] employed this resin in the chromatographic purification of T1, T2r and T2r+ bacteriophages, demonstrating that "bacteriophages may be purified by means of selective adsorption on, and desorption from ECTEOLA anion-exchange adsorbent." A high degree of virus purity was possible, and these investigators suggested that the method might prove of value in "the preparation of other nucleoproteins and viruses." The basic principles underlying the adsorption and elution of bacteriophages and viruses by ionic exchangers have been studied extensively by Puck[4] and his research group, especially with reference to implications concerning hemagglutination phenomena, and the attachment of viruses to red cells.

The April 18, 1958, issue of *Science* carries an interesting and informative article describing "the results of exploratory chromatographic studies

on the purification of several representative animal viruses and rickettsiae.'' The stated purpose of this article by Hoyer, Bolton, Ormsbee, LeBouvier, Ritter, and Larson[5] is to report "that the chromatographic procedure provides high yields of purified infectious agents" and to discuss "some of the implications of the findings for further fundamental and applied research." These investigations were stimulated in the beginning by the success of others using the cellulose ion-exchange columns: Commoner, Taussig and Creaser, and others. Cellulose anion exchangers, ECTEOLA-SF, and DEAE-SF, were employed in the studies by Hoyer and his co-workers for column chromatography and purification of poliomyelitis viruses, Mahoney type 1, Lansing type 2, and Saukett type 3, and of Echo type 13 and Coxsackie type A9 viruses. The virus source in each of these instances was from ultracentrifuged concentrates of tissue-culture fluids derived either from infected monkey-kidney, or from Detroit-98 (D-98) cells. Concentrates of Colorado tick fever virus were prepared from brain tissue of infected moribund suckling mice. Rickettsiae concentrates studied included those of Q-fever and epidemic typhus fever, the concentrates in both instances being derived from infected chick embryo yolk sacs. Several virus preparations were made from appropriately infected tissue cultures in which the virus was cultured in the presence of phosphorus-32, as a means of labeling the virus particles with a radioactive tracer. The preparation methods for the concentrates of virus and rickettsiae, and the ion-exchange column procedures employed are given in some detail by the authors. Titrations, with calculated end points, of the finally resulting suspensions of virus and rickettsiae (i.e., the purified eluates) were carried out appropriately in tenfold serial dilutions in monkey-kidney tissue culture, or in suckling mice (Colorado tick fever virus). In the case of the P^{32}-labeled virus, radioactivity of dried samples was assayed by means of a mica end-window Geiger-Mueller tube with a decimal scaler. The titers of recovered purified virus are given in tabular or graphic form, and an interesting electron micrograph is included which shows Q-fever rickettsiae before adsorption, and a low-magnification field of the purified preparation of Q-fever rickettsiae, obtained as the final product of chromatographic separation.

In a rather critical discussion the authors attempt to evaluate the data obtained in these studies. They feel that column chromatography with cellulose ion exchangers has been employed successfully in the recovery and purification of the mammalian viruses and rickettsiae under study. These agents can be adsorbed onto, and eluted selectively from, ECTEOLA-SF and DEAE-SF columns. The conditions under which this was accomplished seem to permit the recovery of nearly all of the virus added to the columns, yet to allow the removal of much extraneous material. In most individual instances the recovery yield of virus or rickettsiae was considered excellent. Coxsackie A9 and all three types of poliovirus were not so readily adsorbed under the prevailing experimental conditions. This was indicated by their early appearance in the first fractions of the initial eluents recovered; nevertheless, a remarkable degree of purification seemed to be achieved with these strains of virus. Most of the contaminating material can be separated from the infectious particles. Furthermore, extraneous protein material in the suspension can be adsorbed, and also separated from the virus itself. The studies with radioactive phosphorus in the Echo-13 and poliovirus type 2 indicated that marked virus purification had been accomplished. In the case of Q-fever and epidemic typhus fever

rickettsiae, a single adsorption and elution procedure resulted in a striking degree of purification, as demonstrated by electron micrographs. Of particular interest to the authors was the repeated observation that differences in chromatographic behavior exhibited by the various strains of virus and rickettsiae seemed to bear no relationship to particle size, but seemed rather to depend upon the chemical nature of the infectious agents and upon intrinsic differences in their particle surfaces. Of considerable interest also are preliminary investigations in progress which indicate that formaldehyde-treated poliovirus (type 2) can be separated from untreated virus present in the same suspension.

While the experiments reported at this time by Hoyer and his associates are described as "essentially exploratory," those authors express the hope that this relatively simple procedure for the purification and examination of viruses and rickettsiae may prove useful in fundamental investigation as to the nature of these infectious agents, and of value in the preparation of vaccines: both in relation to the purity of the virus strain employed, and with reference to the removal of extraneous protein material of potential danger in sensitivity reactions.

RUSSELL J. BLATTNER

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Correspondence

Pet Peeves

To the Editor:

Inasmuch as your "pet peeves" coincide with mine, I find here just one more reason for keeping you high on my list of Approved Editors.*

During the past decade, I have been feeling increasingly sorry for the Editors of medical journals. You plaintively mention the "Editor who has to read the contributions in manuscript," and the occupational irritations which seem to be mounting. Well, was it Dr. Henry Bowditch who, about a century ago, advised against giving Harvard—yes, Harvard—medical students a written examination on the ground that they couldn't write?

Speaking of the "home of culture and beans," "you wrong me, every way you wrong me," when you imply that I "expect less of a mid-western Editor." It was our mutual friend Llewellyn Sale who first pounced upon the *New England Journal of Medicine's pleonasm*, which proved to be a Source of Innocent Merriment to its distinguished Editor (Blessed be he) and to some of the rest of us. As a Butterer-up of Editors, let me say that you, Sir, are an exemplar of the proverb, "Erudition dwelleth not alone in the Back Bay."

Certainly the past 40 years have seen such a vast accumulation of medical knowledge, all of which must be "borne in mind," "not overlooked," that it is a wonder that more of our medical students and hospital residents aren't what might redundantly be called "literarily illiterate." And here let us pause to pay our respects to those young folk from other lands, so many of whom use our language better than we do.

As you are of course aware, the tendency to (I shall not yield and call it the necessity for) technical specialization is not confined to our own profession. It is exciting enough to encounter M. D.'s who know there is a world—whether of politics, human relations, etc.—who can stop talking about "cases" long enough to discuss various aspects of *Kultur*. It is no less exciting to encounter an engineer or other technical expert who can likewise venture with reasonable safety into other fields.

"Pet peeves?" *Sapristi!* In staff-meetings we think ourselves well off if we don't hear, "He hasn't got any temperature, I don't think," or even, "Lie the baby on the table."

May I mention an as-yet-incipient etymologic monstrosity? It is *cincangiogram*. The Greeks of course had the original word —*kinematos*, meaning motion. Very well, then, the moving angiogram must be a cinemangiogram! All honor to the cardiologists—provided they keep that first *m!*

I suppose we may as well give up on what Dean Briggs used to call "the shallness of the will and the shouldness of the would," —the wanton use of "I would like" for "I should like," etc.

Listing my own pet peeves will doubtless make you more peevish; so I close with Mark Twain's all-too-true comment: "The difference between the right word and the almost right word is the difference between lightning and the lightning-bug."

Sympathetically yours,
PARK JERAULD WHITE

*Any Editor who returns an article of mine with one of those nasty little slips on which he "thanks me for the privilege . . . implying no lack of merit . . ." etc., must expect my disapproval.

To the Editor:

In reading "Severe Neurological Manifestations in Four Children Receiving Compazine (Prochlorperazine)" [J. PEDIAT. 53: 153, 1958], I recalled an unusual case under my care several months ago.

A boy 10 years old was brought to my office because of nervous ties and hostility to his parents. There was no prior history except for mumps two weeks previously and a disturbed home situation. Physical examination was negative. He did manifest some puposeless movements. I put him on syrup of Compazine, 1 dram t. i. d.

Two days later I was called by the mother who was weeping and alarmed because her boy suddenly began to act queer and complain of headaches. A local doctor, called a few hours previously, diagnosed the boy's illness as mumps encephalitis and advised immediate hospitalization.

When I arrived and examined the boy he suddenly cried out "Here it comes," became almost comatose, arched his back and manifested oculogyral symptoms. He had marked opisthotonus, retraction of neck, and severe cyanosis. This lasted a few minutes and he resumed breathing. I had the boy placed in my car and rushed him to the hospital. There he was placed on sedation and oxygen symptomatically. He had two seizures in the car and about fifteen during the next 24 hours. Blood count, spinal fluid, and neurological examinations were normal. However, in view of the history of mumps, a diagnosis of post-mumps encephalitis was made. I was puzzled by the case since none of the cases of mumps encephalitis I had seen had manifested such violent spasms.

After 24 hours his behavior was normal, and he was discharged after one week of hospitalization. Seen about a week ago he was well and had no complaints. The Compazine was discontinued when the boy became ill.

This patient apparently has an idiosyncrasy to the drug, because, with his weight of 80 pounds, a dose of 30 mg. over a 2-day period is within normal range.

I wonder how many doctors have been confronted with similar cases. In this particular case the history of mumps clouded an approach to the diagnosis.

G. S. MEISTER, M.D.

News and Notes

In the *Letter From London* which appeared in the August issue, the next International Congress of Paediatrics was inadvertently referred to as being held in Montreal in 1960.

The date for the Congress is July 19 to 25, 1959, and it will be held at the Queen Elizabeth Hotel.

The **New York Academy of Medicine** will hold its *Second Annual Postgraduate Week* (formerly the Graduate Fortnight), from October 13-17, 1958, inclusive. As last year, the title of the program is Research Contributions to Clinical Practice. The program, as heretofore, will consist of daily evening lectures, a daily afternoon panel meeting, and a Scientific Exhibit. The purpose of the Postgraduate Week is the continuing education of graduate physicians. Although registration is required of non-Fellows of the Academy, no fee will be charged.

The Department of Pediatrics of the *University of Colorado* Medical Center announces **Fellowships in Pediatrics** in Allergy, Infectious Disease, Hematology, and Premature and Newborn Nursery. Applicants should be graduates of approved Schools of Medicine and should have completed at least one or more years of hospital training. Preference will be given to those who are in the course of completing the pediatric hospital training required for the examination of the American Board of Pediatrics. The fellowships, for one or two years, include fundamental laboratory research and clinical investigation, as well as training in clinical diagnosis and management.

Inquiries should be sent to Henry K. Silver, M.D., University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20, Colorado.

The Women's Medical Association of the City of New York offers the **Mary Putnam Jacobi Fellowship** to a graduate woman physician, either American or foreign. This Fellowship will start Oct. 1, 1959, and will amount to $2,000, $1,000 being available Oct. 1, 1959. The recipient of the Fellowship will be expected to make a report to the committee at the end of the fourth month, following which the second $1,000 will be awarded subject to the approval of the committee. The Fellowship is given for medical research, clinical investigation, or postgraduate study in a special field of medicine. The recipient is expected to devote full time to the Fellowship, but exception may be made by the committee under special circumstances. Applications for this Fellowship may be obtained from the secretary of the committee, Ada Chree Reid, M.D., 118 Riverside Drive, New York 24, N. Y., after Aug. 1, 1958, and must be returned before Feb. 1, 1959. Successful candidates will be notified not later than May 1, 1959.

Applications for the **Residency** from July 1, 1959, to Dec. 31, 1959, in **Pediatric Oncology** at *Memorial Center for Cancer and Allied Diseases in New York* will be received up to Nov. 1, 1958. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary: $3,600 annually plus maintenance. For application forms and information write: Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 East 68th Street, New York 21, N. Y.

The *University of Minnesota* announces a continuation course in **Pediatric Radiology** for Radiologists which will be held on the University campus from Nov. 3 to 7, 1958. The course will be held in the Mayo Memorial Auditorium in the University of Minnesota Medical Center on the Minneapolis Campus. Guest participants will include Dr. James B. Arey, Associate Professor of Pathology, Temple University School of Medicine, Philadelphia; Dr. John Caffey, Professor of Radiology, Columbia University College of Physicians and Surgeons, New York City; Dr. Sidney Farber, Professor of Pathology, Harvard Medical School, Boston; Dr. Robert A. Garrett, Professor and Chairman, Department of Urology, Indiana University School of Medicine, Indianapolis; Dr. C. John Hodson, Radiologist, University College Hospital, London, England; Dr. A. S. Johnstone, Professor of Diagnostic Radiology, General Infirmary, Leeds, England; Dr. John A. Kirkpatrick, Jr., Instructor in Radiology, Temple University School of Medicine, Philadelphia; Dr. Edward B. D. Neuhauser, Associate in Radiology, Harvard Medical School, Boston; Dr. Frederic N. Silverman, Director, Division of Roentgenology, The Children's Hospital, Cincinnati; and Dr. E. F. Van Epps, Professor and Head, Department of Radiology, State University of Iowa College of Medicine, Iowa City.

The Course will be presented under the direction of Dr. Harold O. Peterson, Professor and Head, Department of Radiology; Dr. Richard G. Lester, Assistant Professor, and Dr. Samuel B. Feinberg, Clinical Assistant Professor, Department of Radiology. The remainder of the faculty will include members of the faculty of the University of Minnesota Medical School and the Mayo Foundation.

Lodging and meal accommodations are available at the Center for Continuation Study.

Books

Emotional Problems of Adolescents. J. Roswell Gallagher, M.D., and Herbert I. Harris, M.D., New York, 1958, Oxford University Press, 184 pages. Price $3.50.

Hundreds of books have been published on medical or medically related topics addressed to lay readers. While some have been excellent, the majority can be classed as indifferent, and many have been poor and some even bad. While the motivation has usually been an altruistic one of help and education, some have been written for propaganda purposes and a number instigated by publishers to bring out a competitive text in a highly profitable field. As we look back on the scores we have read, only a few stand out clearly in our memory as having been of real value in influencing lay thinking and attitudes. We are of the opinion that another has been written.

In *Emotional Problems of Adolescents* by Drs. Gallagher and Harris, published by the Oxford Press, a new book on this often-discussed theme has been written which we regard as the best that has appeared. It is sound, well written, and avoids the technical psychiatric jargon that detracts from many of the books on the subject written for non-professional readers. This will hardly come as a surprise to those who have been familiar with Dr. Gallagher's work and studies while School Physician at Andover for many years and more recently as Director of the Adolescent Unit of the Children's Medical Center in Boston. Dr. Harris is an Associate at the Unit and Psychiatrist to M.I.T.

The book is not based on a psychologic theory or concept into which an attempt is made to fit the adolescent's problems and emotional reactions but on the great experience of the authors with adolescents. This has led to a remarkable insight and understanding of their problems, of their causes, and how they best should be handled. After an introductory General Statement, the detailed discussion is taken up in eleven chapters: Mental Health; Sex; Achieving Independence; The Severe Disorders; Anxiety States; Psychosomatic Disorders; Homesickness; Pitfalls of Testing; Scholastic Failure; and Antisocial Behavior. Throughout is stressed the realness of his problems to the adolescent, no matter how silly or unimportant they may seem to the adult. Further, that what he needs most is to find some understanding person, such as a teacher or doctor, who he feels is interested in him as an individual and to whom he can talk freely and not simply receive advice and admonition on an ex cathedra basis.

The writing has a clarity frequently lacking in discussions of adolescence for lay readers. The reader is impressed not only by the authors' understanding of, but deep respect for, the adolescent as an individual. In fact the necessity for this is one of the underlying themes that run throughout the discussion of his emotional reactions to the problems encountered. We sincerely hope that the book will be widely read by parents and teachers, as well as by pediatricians. It should be invaluable to teachers in high and preparatory schools who face each day the problems of children of this age. The reviewer has a particular interest in the book because adolescence is a subject he has been interested in and has followed in the literature for many years. We recommend this new discussion without reservation, as it is the most adequate text of its type we have ever read, and regard it as a book of lasting value and importance.

B. S. V.

Common Sense About Gifted Children. Willard Abraham, New York, 1958, Harper & Brothers, 268 pages. Price $5.00.

Professor Abraham's book is timely in view of the current interest in children with superior intelligence. While there is general agreement that their education in school and college should be such as to utilize the superior intellectual endowment, there is wide difference of opinion among educators as to how this should be done. The author has attempted to collect in this volume what we know about gifted children and what is being done for them. Much of our basic knowledge regarding children with a high I.Q. comes from the many years of study and investigations of Terman. The book presents the many ideas, frequently controversial, as to the methods of providing gifted children with an education in keeping with their intelligence, i.e., segregation, acceleration, or combination with the average plus enrichment. It also describes certain community efforts as those of Evanston, Illinois, and the Mede Valley School in Arizona. Today a number of methods are advocated for the education of the gifted child and the author discusses three "big" plans. Professor Abraham groups the gifted child in what is often referred to as "exceptional" children—perhaps best defined as children varying physically or mentally from the average—and stresses the large sums of money being expended for special schools and the education of the handicapped children in this group, in contrast to the expenditure for gifted children. No one will dispute the necessity of providing proper educational facilities for the handicapped from a humanitarian standpoint. There is a current concept that the future of the world depends on the education of the gifted child.

Rehabilitation of the Cardiovascular Patient. Paul D. White, M.D., Howard A. Rusk, M.D., Philip R. Lee, M.D., and Bryan Williams, M.D., New York, 1958, McGraw-Hill Book Co., Inc., 176 pages. Price $7.00.

Four authorities in the fields of cardiology and rehabilitation have collaborated in bringing out this volume. It is estimated that some 9 to 10 million persons in the United States are suffering from some disease of the heart or cardiovascular system, and patients with these conditions form an increasingly large part of the 2 million persons needing vocational rehabilitation in order to perform gainful work. After an historical introduction, chapters follow on the particular types of cardiac and vascular lesions. These include rheumatic fever and rheumatic heart disease of interest to the pediatrician. The chapter entitled "Congenital Heart Disease" is more in the nature of a general discussion of the problems of the congenital cardiac patient than a discussion of his rehabilitation. No program of specific rehabilitation is outlined, and the reviewer agrees with the apparent although unstated attitude of the authors that this is next to impossible except in conditions amenable to surgery.

Surgery in Infancy and Childhood. Matthew White and Wallace M. Dennison, Baltimore, 1958, Williams & Wilkins Co., 444 pages. Price $9.50.

This handbook by Matthew White and Wallace M. Dennison, both from Glasgow, Scotland, is a rather unique book in that the entire field of pediatric surgery is compressed into 400 pages. Practically every surgical problem arising during childhood is mentioned. Some subjects are covered in one short paragraph, but what is said is clear and to the point. The book obviously is not intended to be a reference work—in fact no references to medical literature are included—but rather a simple and quick guide to those who want concise information about the basic facts of pediatric surgery and all its subspecialties. The authors have stated their views clearly and spent no words discussing controversial opinions.

Perhaps the greatest virtue of this book is that it will acquaint the reader with what is being done surgically for children today. Although the book has been written primarily for general practitioners and medical students, those who are familiar with the problems of pediatric surgery will find a number of helpful hints and some very sound advice in its pages.

The entire field of pediatric surgery from cephalhematoma to flatfoot is covered in this neatly packed book which is recommended for medical students who wish their fare dished up in small compact servings and for

general practitioners and those in other specialties who want to know what is being done for various surgical conditions arising during childhood. This book supports the observation that much can be said in a few words.

W. J. P.

The Medical Assistant. Miriam Bredow, New York, 1958, McGraw-Hill Book Co., Inc., 430 pages. Price $7.50.

The author, Dean of Women at the Eastern School for Physicians' Aides in New York, is the author of an excellent earlier text entitled *Handbook for the Medical Secretary.* This volume is planned for the medical assistant in the doctor's office and covers the material which, in her experience, the medical assistant must know: physical therapy, sterilization, first aid, office surgery, and similar topics. It is a timely subject as medical assistants are being increasingly used in physicians' offices. The duties of an assistant will vary according to the particular specialty, and many physicians therefore have trained their own office assistants to meet their needs.

Étude radiologique de la circulation veineuse du membre supérieur (sujet normal). E. Lavizzari and V. Ottolini, Paris, 1958, Masson et Cie, 122 pages. Price 2,400 fr. (French).

A monograph from the Institute of Radiology at the University of Milan. An unusually fine technical study of the veins of the upper extremities of the normal subject made by means of phlebograms. Beautifully illustrated. Of special rather than general interest.

Our Nuclear Adventure. D. G. Arnott, New York, 1958, Philosophical Library, 170 pages. Price $6.00.

Those interested or worried about the "possibilities and perils" of nuclear power, as the subheading of the book states, will find a lot of information in this volume. The author is British and is decidedly censorius of the political and social aspects of the development of nuclear power in his country.

Cleft Palate and Speech, ed. 4. Muriel E. Morley, Edinburgh, 1958, E. & S. Livingstone, Ltd., 271 pages. Price $6.50. (Williams & Wilkins Co., U.S. agents.)

A new revised edition. The last was published in 1954.

Growth and Development of the Young Child, ed. 6. Marian E. Breckenridge and Margaret Nesbitt Murphy, Philadelphia, 1958, W. B. Saunders Co., 548 pages. Price $5.50.

A new revised edition (last in 1953) of this well-known text used in many college courses on child development.

Erratum

In the article entitled "Pediatric Use of Antibacterial Agents" by C. Henry Kempe, M.D., which appeared in the July issue of the Journal, the following corrections should be made in Table I:

On page 21, Ristocetin dose should read 12 mg./lb./day.

On page 22, Isoniazid dose should read 8 mg./lb./day (in 2 doses). Intramuscular should read 5 mg./lb./day (in 2 doses).

Editor's Column

VISITING POLICIES FOR CHILDREN'S HOSPITALS

A FEW years ago the JOURNAL* published a report of the visiting policies in a group of children's hospitals in New York City as of 1954. The Citizens' Committee for Children of New York City, which made the original report, has recently rechecked the same hospitals, and the progress that has been made in the liberalization of visiting hours is quite interesting. The original group of 75 hospitals surveyed has been reduced to 64 through hospital mergers and closures and the discontinuance of pediatric departments. The following table taken from the recent report shows not only the changes that have occurred by number of hospitals between 1954 and 1958 but as related to the number of pediatric beds.

It will be noted among other changes that twice the number of hospitals now allow visiting seven days in the week, and this applies to an increase of nearly 150 per cent in the number of beds.

A wide variation exists, according to the report, in the number of hours for visiting and in the designated time when visiting is allowed. There is a trend to split schedules: 10 A.M. to 12, and 2 to 5 P.M.; 11 A.M. to 2:30 P.M. and 5 to 6:30 P.M.; 11 A.M. to 1 P.M. and 3 to 7 P.M. A few have one long period such as noon to 6 P.M. and 11 A.M. to 7 P.M. Conditions vary in different hospitals, depending on such factors as size, location, and the hospital staff and personnel. Obviously, each hospital has worked out a plan for liberalization to meet its particular situation. In only two of the 64 hospitals were the visiting hours curtailed. In one the hours were changed from

TABLE I

NUMBER OF VISITING DAYS PER WEEK	HOSPITALS				CHILDREN'S BEDS			
	1954		1958		1954		1958	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
7	24	(32)	41	(64½)	825	(23)	2,207	(57)
6	—	—	1	(1½)	—	—	18	(½)
5	2	(3)	—	—	47	(1)	—	—
4	4	(5)	2	(3)	129	(4)	74	(2)
3	19	(25)	10	(15½)	971	(26)	677	(17)
2	23	(31)	10	(15½)	1,314	(36)	897	(23½)
1	3	(4)	—	—	380	(10)	—	—
TOTAL	75	(100)	64	(100)	3,666	(100)	3,873	(100)

*J. PEDIAT. 48: 710, 1955.

2 to 5 P.M. to 2 to 3 P.M. three times a week, and in another with an unusually liberal schedule in 1954 of 10 A.M. to 8 P.M., a change was made to 11 A.M. to 1 P.M. and 3 to 7 P.M. daily. We are familiar with hospitals in other parts of the country that jumped to almost unlimited hours a few years ago under the trend to liberalization only to find it necessary to return to definite split periods, although these reflected an increase in the total number of visiting hours when compared with the hours allowed in past years. Probably most of our children's hospitals continue the custom of past years which allows increased visiting for parents with children on the "seriously ill list," and around-the-clock visiting when the child is considered dangerously ill.

The report discusses certain questions that have been raised in regard to liberalized visiting without going into the details of the sources forming the basis of the conclusions. The report simply categorically states that an increase in cross-infection has not occurred. It states further that an abuse by parents of a liberalized policy has not happened. A third question considers the fear of a liberalized policy of visiting interfering with ward rounds in teaching hospitals, treatment procedures, etc. The Committee reports, "Quite the opposite is the case." We know of hospitals that had changed to a wide-open "all-day" policy, and found it necessary to go back to a policy of no visiting during certain hours because of interference with the hospital work.

No one questions the advantages and desirability of liberalization of the visiting hours for parents of hospitalized children, and the New York City report brings out the changed attitude and progress that has been made in the last few years. On the other hand, the viewpoint of some extremists —probably the necessary evil in any movement—urging unrestricted, unlimited visiting for psychological reasons is not tenable, as it ignores the fact that children are hospitalized for physical illness, and the primary purpose of the hospital is to treat these illnesses. It reminds one in some ways of the "progressive" educational faddists of a few years ago, who would remove all discipline from the young growing child in order that he might develop his own individuality and personality and find "freedom of expression," completely ignoring the fact that every individual must adjust his life to a complicated world, and that discipline is necessary if this adjustment is to be a sound and happy one.

The liberalization of visiting hours for children's hospitals is most desirable. Just how liberal, is a matter that each hospital must decide for itself, as the extent to which it is desirable depends on a number of factors which vary from hospital to hospital. Of particular importance among these are the type of disease or patient for which the hospital is organized, the size and location of the hospital, matters involving the hospital staff and personnel, and the activities of the hospital aside from the immediate care of the patient.